IN THIS ISSUE

13 Stroke and seizure continue to be the major brunt of in patient neurology care. An observation from teaching hospital Azra et al

18 Demographic and histopathological patterns of neuro-epithelial brain tumors in Eastern Province of Saudi Arabia Taha et al

23 Comparison of 2 methods of neuropathic pain assessment in carpal tunnel syndrome and hand functions Ceceli et al
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CONTENTS

REVIEW ARTICLE

An overview of complications affecting the Central Nervous System following bariatric surgery
AZRA ZAFAR, ISMAIL A. KHATRI .......................................................................................................................... 4

ORIGINAL ARTICLES

Stroke and seizure continue to be the major brunt of in patient neurology care. An observation from teaching hospital

Demographic and histopathological patterns of neuro-epithelial brain tumors in Eastern Province of Saudi Arabia
M. S. TAH, F. M. ALMSNED, M. A. HASSEN, I. M. ATEAN, A. M. ALWBARI, Q. K. ALHARBI, M. M. ABDULKADER, H. S. ALMUHAISH ........................................................................................................................................................................... 18

Comparison of 2 methods of neuropathic pain assessment in carpal tunnel syndrome and hand functions
E. CECELI, S. GÜMRÜK, M. OKUMUŞ, S. KOCAOĞLU, H. GÖKSU, A. KARAGOZ .................................................................................................................................................................................................................................................................................................................. 23

APOE Gene polymorphism among Jordanian Alzheimer's patients with relation to lipid profile

Endoscopic transsphenoidal approach to skull base lesions. A clinical prospective study
MONEER K. FARAJ, WISSAM J. SAGBAN .............................................................................................................. 35

How do physical capacity, fatigue and performance differ in children with duchenne muscular dystrophy compared with their healthy peers?
AKMER MUTLU, HALIL ALKAN, TÜZÜN FIRAT, AYNUR A. KARADUMAN, ÖZNUR T. YILMAZ ......................................................... 39

Perioperative lumbar drain utilization in transsphenoidal pituitary resection
SHATHA ALHARBI, GRIFFITH HARSH, ABDULRAZZAG AJLAN .......................................................................................... 46

CASE REPORTS

Encephalopathy mimicking non-convulsive status Epilepticus
RAMACHANDIRAN NANDHAGOPAL, FATHIYA AL-MURSHAREDI, MUJAHID AL-BUSAIDI, AMNA ALBUSAIID .................................................................................................................................................................................................................................................................................................................. 52

Sialidosis type I presenting with a novel mutation and advanced neuroimaging features
MURAT GÜLTEKIN, RUSLAN BAYRAMOV, CAGATAY KARACA, NIYAZİ ACER ........................................................................................................................................................................................................................................................................................................... 57

BRIEF COMMUNICATION

Respiratory support attitudes among pediatric intensive care staff for spinal muscular atrophy patients in Saudi Arabia
Mohamad-Hani A. Temsah, F. M. Al-Sohime, F. A. Bashiri, A. A. Al-Eyadhy, G. M. Hasan, A. A. Alhaboob .............. 62

The clinical features of patients concurrent with Guillain-Barré syndrome and myasthenia gravis
JUNLIANG YUAN, JUAN ZHANG, BINGWEI ZHANG, WENLI HU ................................................................................. 66

www.neurosciencesjournal.org Neurosciences 2018; Vol. 23 (1) A1
CORRESPONDENCE

Type and etiology of pediatric epilepsy in Jordan. A multi-center study
MAHMOOD D. AL-MENDALAWI ........................................................................................................................ 71
REPLY: ABDELKARIM A. AL-QUDAH ....................................................................................................... 71

Cochrane library newsalert

Maternal mortality rates are on the rise, but more accurate estimates are needed ........................................ 73
Past falls can help predict an individual’s risk of bone fracture independent of other factors ....................... 73

WHO Press Release

Up to 650 000 people die of respiratory diseases linked to seasonal flu each year ........................................ 74
Dementia: number of people affected to triple in next 30 years .................................................................... 75

Instructions to Authors ........................................................................................................................................... 75

Appointments .......................................................................................................................................................... 82
Neurosciences journal is now in its 23rd year and since its establishment the journal has been improved in the contents, quality and the circulation around the world.

In 2017, we invited all the local societies related to neurosciences field to set an agreement between the journal and the society. The society should contribute to the journal scientifically and the journal will be the official journal to the society in return. We congratulate both Pan Arab Union of Neurological Societies and Saudi Association of Neurological Surgery to be the affiliated societies in our journal and we are looking forward for more contribution.

In 2018, we aim to increase the number of issues to meet the increased load of manuscripts. Our objective is to enrich the scientific Neuroscience material presented by the journal with important topic reviews and regular neuroscience quizzes to achieve high citations. We will continue to promote our new web-based manuscript submission interface; strive to reduce the time from received to acceptance and acceptance to publication to no more than 3 to 4 months each; attend regional conferences, and participate in academic activities to encourage submission of high quality articles; and commission our best reviewers to write good articles and encourage editorial board members to contribute material for a regular editorial feature on topical issues. The journal also is introducing a new look, and a new logo. We also change the layout of the journal. We also plan for a web based manuscript submission interface system.

The journal started the implementation of CARE Case Report Guideline1 as a mandatory requirement for case report submissions. Prior to submission, authors should read the CARE Checklist and write the article following the guideline's essential requirements. This hopes to raise the clinical value of case reports published.

We are also conducting a regular critical auditing to the performance of the Journal. We are very meticulous with regards to the accuracy of the editing; medical writing is different from other professional writing, an excellent scientific experiment with novel ideas may still be rejected due to poor writing. Most authors in this region have difficulty in incorporating the objective, methods and knowledge in a proper English language.

The editors observed that poor language quality is one of the factors that delays the peer review process. Occasionally, reviewers were unable to assess the paper due to poor writing. Language should not be a barrier in scientific publication especially for non-native English speakers. Subsequently, articles with language deficiencies also take significant time in the editing stage and delay the publication process. To overcome this, we strongly suggest that prior to submission, authors should have their articles edited for correct use of grammar, syntax, flow and clarity and submit only once the language has been improved. As a pre-submission requirement, strict compliance shall be observed.

Figure 1 - Number and type of manuscripts processed for the year 2017.
Editorial Message

The discoverability and accessibility of scientific content to various relevant platforms is very important in today’s digital age. We take this time to announce the indexing of Neurosciences Journal in Cengage. Cengage Company is a global leader with thousands of partner libraries around the world and has a large digital archive of research databases, reference books, eBooks and more. With the recent inclusion in this database, we anticipate enhanced visibility and accessibility of our articles.

In 2017, we received a total number of 159 manuscripts, with an average rejection rate of 27%. Reasons for rejection included papers out the scope of the journal, of low scientific quality, not meeting the requirements of the journal, authors failing to submit the revisions and other necessary requirements, and duplicate publication. However, over 4 issues of 2017, we published a total number of 55 articles which include: 21 originals, 1 editorial, 5 reviews, 2 systematic reviews, 12 case reports, 2 clinical notes, 6 brief communications, 2 correspondences, 1 clinical practice guidelines and 3 MCQs. The average processing time from received to acceptance was 3.35 (1-10) months, mode=2 months, 3.28 (1-8) months from acceptance to publication and 6.63 months from received to publications (3-15) months mode=6 months. Fifty-three percent of published articles were from KSA, with 7% from Turkey, 15% from China, 4% from Iraq and 4% from Jordan. The remaining 17% of published articles we received from UK, Germany, Oman, India, Iran, Nigeria, and Pakistan.

We extend our thanks to the Editorial and Advisory Board Members for their significant contributions to maintaining the standards of the journal, and we look forward to their important continued role in achieving our goals for 2018. We would like to thank the outgoing Advisory Board member (Mohamed Tariq) who had now finished his term and would like to welcome Brahim Tabarki and Joseph Lamanna to the Advisory Board. We also extend our thanks to the outgoing Editorial Board members. We are honored they have agreed to join the board, and their individual contributions will be of great value to the journal. We continue the international diversity of members that the current board offers. We hope all our readers continue to benefit from the published material, and we extend our sincerest thanks to our authors, readers, reviewers, and board members, and wish all a successful year.

References

1. CARE. Case reports guidelines. [Updated 2018; Accessed 2017 November 14]. Available from URL: http://www.care-statement.org/
Our thanks also go to the following reviewers, who have participated in the excellent review of manuscripts and books for the year 2017.

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*Reviewers who reviewed 3 or more articles for the year 2017
An overview of complications affecting the Central Nervous System following bariatric surgery

Azra Zafar, FCPS Med, FCPS Neurology, Ismail A. Khatri, MD, FAAN.

ABSTRACT

Bariatric surgery has been considered as an effective treatment for morbid obesity. Apart from procedures related complications, a broad spectrum of neurological disorders affecting any part of neuraxis has been reported following BS. Central nervous system complications, although less common than peripheral nervous system complications, carry significant morbidity and potential mortality. Encephalopathy, behavioral and psychiatric disorders, myelopathy and optic neuropathy are the most frequently reported CNS complications. Early detection and prompt management may improve or completely reverse these neurological complications. It is essential that the treating physicians must be aware of their clinical manifestations and management, so early diagnosis and treatment can prevent patients from suffering significant neurological deficits and even death. This review discusses the clinical manifestations of these complications in detail which will help concerned physician in earlier recognition and hence prevent the delay in specific treatment.

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Obesity and its hazards. Obesity is a pathological condition characterized by accumulation and maintenance of excessive adipose tissue. Obesity is often assessed by body mass index (BMI) values, where a BMI of 30 kg/m² or more is considered obesity, while BMI value between 25 and 29.9 kg/m² is considered overweight. The terminology of overweight, obesity and severe obesity are continuum of a spectrum. Obesity is among one of the major risk factors for cardiovascular and cancer morbidity and mortality contributing to almost 3 million deaths every year worldwide. It is associated with an increased prevalence of morbidity and reduced life expectancy. The mortality risk associated with obesity was recognized even in the works of Hippocrates.

A number of comorbidities have been associated to obesity including coronary artery disease, hypertension, stroke, a variety of cancers, non-insulin dependent diabetes mellitus, gall bladder disease, lipid disorders, osteoarthritis, and pulmonary diseases including sleep apnea as well as gout. Obesity has a negative impact on vascular risk factors and has not only been attributed to stroke but also to neurodegenerative disorders including dementia. Leptin, which is considered as anti-obesity hormone is also thought to have preventive effect on neuronal death and with increasing age, as the levels of circulating leptin decrease, the process of neurodegeneration can accelerate.

Epidemiology of obesity. Obesity is not the problem of individuals. Obesity has reached pandemic proportions. The 2014 WHO facts sheet suggests that about 13% of world population is obese, with more than 1.9 billion adults 18 years and above being overweight. More alarming is the trend with doubling in worldwide prevalence of obesity between 1980 and 2014. Approximately 41 million children under the age of 5 were obese in 2014, with more than half of those living in Asia. Not only that, the mortality from obesity and overweight is more than the deaths from underweight. The rate of obesity and corresponding obesity associated disease burden has increased in past several decades despite countless research studies, national statements and efforts from worldwide organizations.

Bariatric surgery: an overview. Obesity is highly preventable through healthier food selection and the implementation of regular physical activity. Surgical therapy for the management of obesity is recommended for people with BMI of ≥40 kg/m² or for those with BMI ≥35 kg/m² with additional obesity related complications like hypertension, type 2 diabetes mellitus, dyslipidemia, or obstructive sleep apnea. However, tremendous increases in demand for weight loss and the advancement in bariatric surgical procedures and techniques have made BS the most efficacious treatment for morbid obesity. Little over 340,000 bariatric surgeries were performed in the year 2011 by more than 6500 bariatric surgeons across the world. A
number of surgical methods have been tried over past 50 years, many of those abandoned now. Currently the most commonly used methods are sleeve gastrectomy (SG), Roux-en-Y gastric bypass (RYGB), adjustable gastric banding (AGB), and biliopancreatic diversion/duodenal switch (BPD/DS).4,12 These are shown in Figure 1. In addition to surgical management, a number of endoscopic procedures have also been developed using intragastric balloons, sutures, and absorbptive techniques such as botulinum toxin.13

The primary aims of surgery are restriction of food intake and/or iatrogenic malabsorption of food.5 A number of mechanisms have been suggested to explain the weight loss accomplished by BS. Restriction of food intake due to small volume of the stomach pouch is a major contributor, resulting in decreased calories. Decreased nutrient absorption was considered an added mechanism.14 The decreased appetite and early satiety may not only be due to the decrease in the stomach space, but may also be contributed by neuronal and hormonal modulation.4 The so-called enteroencephalic endocrine axis is considered to contribute significantly through complex interactions between centers in the brain and hormone productions in the intestinal tract, as well as pancreas.14 Bariatric and metabolic surgery have shown to improve or resolve many obesity related complications and improve survival as well.15

**Benefits of bariatric surgery.** The outcomes following bariatric surgery vary between procedures, and predicting individual outcome is difficult. However, a number of conditions have been shown to improve after BS including cardiovascular health, systemic hypertension, diabetes mellitus, sleep apnea, lipid profile, as well as nonalcoholic fatty liver disease.4 Both fatal and non-fatal myocardial infarctions and strokes are reduced after BS.16 The incidence of first time cancer, and cancer related diagnosis appears to be decreased after BS.17,18 This risk reduction appears to be independent of the type of cancer, whether the cancer is considered obesity related or unrelated. The overall mortality, development of comorbid conditions and overall healthcare use have all been shown to be reduced after BS.19

**Complications of bariatric surgery.** Though clearly offering benefits to morbidly obese, BS is not a completely benign procedure. A number of complications of BS have been reported including death. Short or long term complication rates around 20% have been reported.20 Increasing expertise, safer methods, and use of laparoscopic procedures seem to have decreased the morbidity significantly.21 The initial reports suggested nearly 2% mortality risk, which over time has improved and mortality rate as low as 0.3% has been reported.22,23 Sepsis secondary to anastomosis leak, cardiac events and pulmonary emboli are the main cause of 30-day mortality.24

Apart from perioperative complications related to surgical procedures, BS is associated with significant gastrointestinal, metabolic, nutritional and neurological complications. Deficiencies of iron, and other essential elements, thiamine (vitamin B1), cobalamin (vitamin B12), folic acid and fat soluble vitamins can occur after BS. The risk of nutritional deficiencies depends on postoperative weight loss, the surgical procedure performed and patient compliance with follow up.25 Nutrient deficiencies that occur after BS are probably the most important long term complications as they may lead to potentially irreversible hematological, metabolic and neurological conditions.26

**Neurological complications.** Neurological complications occurring in BS are not uncommon. These complications have been reported to occur in 5-10% of patients after BS.27 Recently, a cross sectional study from Jeddah, KSA reported the rate of 3% (15) among 451 patients undergoing BS.28 In another retrospective study involving 592 post sleeve gastrectomy patients, only 7 (1.18%) were found to have neurological complications.29 Almost any region of the nervous system can be affected.27,30 These complications can be early or delayed and can occur months to several years after surgery. A number of neurological complications including encephalopathy, psychiatric disorders, behavioral changes, ataxia, myelopathy, optic neuropathy, plexopathy, peripheral polyneuropathy, mononeuropathy, myopathy, myotonia, and compartment syndrome have been described.27 Wernicke’s encephalopathy and polyneuropathy due to vitamin B1 deficiency can present within few days to weeks after BS and often proceed by intractable vomiting. While myelopathy and neuropathy secondary to vitamin B12 deficiency may take years to develop.

**Patterns of neurological complications.** The neurological complications of BS had been classified in various ways based on timings, early versus late; site of involvement, peripheral versus central; and mechanism.31 Frequently, more than one part of neuraxis is involved.32 Early complications can manifest within days and weeks and include peripheral nerve damage due to stretch or compression injury, Wernicke’s encephalopathy and polyneuropathy or polyradiculoneuropathy. Late complications may only manifest after several years of surgery and include optic neuropathy, myelopathy, peripheral neuropathy and myopathy. In this paper, the neurological complications affecting CNS are reviewed according to site of involvement. Table 1 summarizes the various identified CNS complications after BS.
Mechanisms of neurological complications. The most common underlying mechanism of neurological complications is nutritional deficiencies. Acute weight loss resulting in susceptibility to compression neuropathies is another mechanism. The patient undergoing BS, despite their obesity may have subclinical or overt nutritional deficiencies. After the surgery, the malabsorption results from a variety of mechanisms including decreased gastric acidity, decreased absorption due to bypass of proximal intestine, short food contact time, diarrhea, blind loop syndrome and deficiency of factors required for absorption of certain nutrients resulting from loss of functional gastrointestinal tract. Vitamin B12, thiamine, and copper are the commonest micronutrients involved in neurological complications, however, other potential but uncertain contributors include vitamins like folate, pyridoxine, riboflavin, vitamin D and vitamin E, minerals like calcium phosphorus and magnesium, and trace elements like zinc, iodine and selenium. Table 2 summarizes the potential mechanism and involved micronutrient in CNS complications of BS.

Central nervous system complications of bariatric surgery. Wernicke's Korsakoff syndrome (WKS), episodic encephalopathy associated with D-lactic acidosis, behavioral changes and neuropsychiatric disorders, CNS demyelination, myelopathy, myeloneuropathy, and optic neuropathy are some of the reported CNS complications. The relationship of stroke and seizures is still less well defined. Some of the reported complications as stroke, CNS demyelination and cognitive impairment following BS need to be verified by further randomized trials. Diagnostic findings and treatment of common CNS complications are outlined in Table 3.

Wernicke's Korsakoff Syndrome (WKS). Wernicke's Korsakoff syndrome is the best known neurological complications of thiamine (vitamin B1) deficiency. Wernicke's encephalopathy (WE) characterized by acute confusion, ataxia and nystagmus was described in late 19th century. Korsakoff syndrome (KS) is a sequela of WE seen in about 80 percent of survivors of Wernicke's encephalopathy. The characteristic features of KS are anterograde amnesia, retrograde amnesia, confabulation (invention of new memories), apathy and lack of insight. Classically, Wernicke's encephalopathy and KS have been described in relation to intractable vomiting, hyperemesis gravidarum and excessive alcohol intake. KS is more likely to be seen when WE is related to alcohol abuse.

A relatively uncommon condition in modern world, WE has emerged as a serious and significant complication of BS. The exact incidence of WE after BS is unknown, however, more than 100 cases have been reported in literature. In an early series of 500 patients with BS, 0.4% patients developed WE. Systemic reviews discussing WE after BS have reported finding in 32 and 84 cases. More than 80% cases were women in both reviews with onset of symptoms between 2 weeks to 18 months of surgery. It happened after all modalities of BS and the patients had between 13-45%
weight loss at the time of diagnosis. Recurrent vomiting for several days was the precipitant in most cases. In the patients who did not have recurrent vomiting, avoidance of food, poor appetite, rapid weight loss and noncompliance with vitamin supplementation were the possible precipitants. The classic triad of confusion, ataxia, and eye signs is not always present in these patients. Several additional neurological symptoms and signs including third and sixth cranial nerve palsies, dysarthria, dysmetria, myoclonus, seizures, psychiatric symptoms, vestibular symptoms, blurred vision, papilledema and gait disturbances were seen. Polyneuropathy is often an associated complication. The entire spectrum may not be solely explained by the deficiency of thiamine and additional inflammatory mechanisms may play a role.

Thiamine is a water soluble vitamin that has small reserves in the body and can be depleted in less than 3 weeks with decreased oral intake. The diagnosis remains mainly clinical, supported by laboratory and imaging studies. Serum and urine thiamine levels after BS are not reliable indicators of tissue levels. Red blood cell assays of relevant enzymes may be more sensitive indicators. MRI brain is the imaging modality of choice, although it may be normal in some cases. The typical abnormalities are seen in periventricular region, thalamus, hypothalamus, mammillary bodies, periaqueductal region, as well as other parts of brainstem and cerebellum. Rarely corpus callosum and basal ganglia may be involved. Untreated, the condition may be fatal. The treatment regimen is not very well defined; however, parenteral treatment is mostly recommended. Patients at risk should get parenteral thiamine before administration of glucose. In cases with established thiamine deficiency, supplementation with 30 mg twice daily for several months should be considered. In the reported literature of WE after BS, more than half of the patients made complete recovery. Those with incomplete recovery had residual cognitive deficits, psychosis, gait disturbances, and nystagmus. Fortunately, death was a rare complication.

### Encephalopathy associated with D-lactic acidosis

Few reports of encephalopathy characterized by episodes of confusion, behavioral abnormalities, weakness, lethargy, ataxia and dysarthria in association with D-lactic acidosis have been described after jujnenoleostomy. The neurological symptoms often precipitated after high carbohydrate diets and believed to result from fermentation of carbohydrates in the colon or bypassed segment of the small bowel resulting in elevated levels of D-lactate. Although severe metabolic acidosis was considered to be associated with this condition, the serum chemistries and absence of anion gap may be misleading. Diagnosis is established by marked increase in D-lactate concentration in serum and urine. It is of note that most laboratories routinely check L-lactate and do not check the D-lactate levels. When this condition is suspected, D-lactate levels should be determined as L-lactate levels may be normal. High carbohydrate ingestion can reproduce

### Table 3 - Diagnosis and treatment of common central nervous system complications.

<table>
<thead>
<tr>
<th>Complications</th>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wernicke’s encephalopathy</td>
<td>Clinical</td>
<td>Intravenous thiamine 500 mg 3 times a day for 2-3 days followed by 250 mg daily for 3-5 days, 32,36,38</td>
</tr>
<tr>
<td></td>
<td>Erythrocyte transketolase activation assay or RBC thiamine diphosphate</td>
<td>Oral maintenance dose of 50-100 mg daily for long term</td>
</tr>
<tr>
<td></td>
<td>Characteristic paraventricular signals on MRI</td>
<td>Correction of metabolic acidosis</td>
</tr>
<tr>
<td>Encephalopathy associated with D-lactic</td>
<td>Elevated D-lactate levels in serum and urine</td>
<td>Carbohydrate restriction</td>
</tr>
<tr>
<td>acidosis:</td>
<td>High an ion gap metabolic acidosis</td>
<td>Antibiotics</td>
</tr>
<tr>
<td>Hyperammonemic</td>
<td>Measurement of plasma ammonia, zinc, glutamine and serum albumin level</td>
<td>Dietary protein restriction</td>
</tr>
<tr>
<td>encephalopathy (HAE)</td>
<td>along with genetic testing for OTC enzyme deficiency</td>
<td>Parenteral glucose and lipid infusion</td>
</tr>
<tr>
<td>Myelopathy secondary to vitamin B12</td>
<td>Serum B12, methylmalonic and plasma homocysteine levels</td>
<td>Repletion of zinc, other micronutrients and amino acids.</td>
</tr>
<tr>
<td>deficiency</td>
<td>Abnormal signals in dorsal column and corticospinal tract on MRI</td>
<td>Hemodialysis</td>
</tr>
<tr>
<td>Myelopathy secondary to copper deficiency</td>
<td>Serum and urinary copper activity</td>
<td>Reversal of surgical procedure</td>
</tr>
<tr>
<td></td>
<td>MRI findings similar to B12 deficiency</td>
<td></td>
</tr>
<tr>
<td>Myelopathy secondary to folate deficiency</td>
<td>RBCs folate</td>
<td>Parenteral; 1-5 mg daily</td>
</tr>
</tbody>
</table>

RBC - red blood cells, MRI - Magnetic resonance imaging, HAE - Hyperammonemic encephalopathy, OTC - Ornithine transcarbamylase
the condition, whereas fasting and administration of intravenous amino acids reverses the metabolic changes and improves symptoms.\textsuperscript{40} A case report published in 2000 reported the occurrence of the condition 23 years post-surgery\textsuperscript{42} and another in 2017 reported it in a 48 years old woman 4 years after BS.\textsuperscript{43} The condition has been treated with correction of metabolic acidosis, carbohydrate restriction or fasting and antibiotics acting on gut flora.\textsuperscript{43} This condition should always be considered as an important differential diagnosis in cases of episodic confusion with no other explained etiology.

Hyperammonemic encephalopathy (HAE). Hyperammonemic encephalopathy has been recognized as a serious and potentially treatable CNS complications following gastric BS. Nearly 25 cases of HAE have been reported following RYGB in the absence of overt hepatic disease.\textsuperscript{44} It is hypothesized that nutritional complications following gastric BS may unmask preexisting subclinical urea cycle disorder such as ornithine transcarbamylase deficiency (OTC) which can lead to fatal hyperammonemia.\textsuperscript{45-47} In a retrospective review of 20 patients with gastric bypass associated hyperammonemia (GaBHA), 95\% of patients were female. Weight loss, HAE associated with increased plasma glutamine levels, lack of evidence of cirrhosis, low serum albumin levels and reduced plasma zinc levels were commonly identified features. Mortality rate as high as 50\% has been reported.\textsuperscript{48} Measurement of plasma ammonia, zinc, glutamine and serum albumin level along with genetic testing for OTC enzyme deficiency helps in early diagnosis of this clinical entity which carries high mortality rate. Dietary protein restriction, parenteral glucose and lipid infusion along with repletion of zinc, other micronutrients and amino acids is the mainstay of treatment. Hemodialysis is done in refractory cases.\textsuperscript{44} Reversal of surgical procedure may be one option.\textsuperscript{49}

Neuropsychiatric disorders. Several neuropsychiatric and psychobehavioral disorders have been described in relation to BS. Many of the patients have existing psychological conditions prior to BS. Mood disorders, anxiety disorders and binge eating disorder comprise the large majority of pre-existing conditions in this population.\textsuperscript{50} Improvement in psychopathology after BS has been reported in studies.\textsuperscript{51,52} However, psychiatric disorders may appear following BS as well. Frank eating disorders like anorexia nervosa and bulimia are not uncommon. Few patients develop eating avoidance post surgically, the so called postsurgical eating avoidance disorder.\textsuperscript{53} Some patients with pre-surgical binge eating disorder may resort to binge eating behavior, however, gastric restrictions limits the ingestion of large amounts. Night eating syndrome, in which there is a potential circadian shift of eating and sleep, appears to decrease after BS.\textsuperscript{54}

Alcohol use and other substance use disorder probably do not change much after BS. In a cohort of about 2000 patients, the alcohol use disorder was more common in the second postoperative year, compared to the first postoperative year and the year prior to surgery.\textsuperscript{55} There is inconclusive evidence about other addictive behaviors like gambling, compulsive shopping, and compulsive sexual behavior.\textsuperscript{53}

The risk of suicide is higher in bariatric BS patients. Tindle et al\textsuperscript{56} reported the suicide rate as high as 6.6/10,000, while another systematic review of 28 studies reported a rate of suicide as 4.1/10,000. The suicide was usually committed between 18 months to 5 years postoperatively. Pre-existing psychiatric conditions, particularly long-term depression were the most plausible explanation for this finding.\textsuperscript{57} Acute mania has been reported by Nepal et al\textsuperscript{58} in 57 years old female 2 months after RYGB. Pre-surgical psychiatric evaluation before BS is recommended to monitor the at risk patients.\textsuperscript{53} Pre surgical counseling and psychoeducation should be planned for patients with suicide risk. Pharmacotherapy and psychotherapy should be implemented where indicated.\textsuperscript{59}

Stroke and seizure. Stroke and seizure are not common after BS. A case of stroke and seizure 4 months post gastric bypass surgery had other risk factors for strokes and malnutrition and dehydration were the possible precipitant.\textsuperscript{60} This finding needs to be confirmed by further studies.

Central nervous system demyelination. Central nervous system demyelination resembling multiple sclerosis (MS) has been described after BS. A study from Brazil describing 26 patients with neurological complications identified CNS demyelination in five patients. MRI in four cases fulfilled diagnostic criteria for multiple sclerosis. However it was not well established that the findings were an effect of BS, or incidental co-existing multiple sclerosis.\textsuperscript{61} Monophasic CNS demyelination was reported in 2 and relapsing and remitting MS in 1 out of 15 patients with neurological complications after BS by Falah et al.\textsuperscript{62}

Cognitive impairment and bariatric surgery. Higher midlife BMI has been identified as an independent risk factor for dementia such as Alzheimer’s disease and vascular dementia.\textsuperscript{63} Changes in cognitive abilities may begin in childhood. Blanco-Gomez et al\textsuperscript{64} reported greater deficit in inhibitory control in overweight and obese children compared with age-matched and gender-
matched controls. BS has been shown to improve cognitive function rapidly after surgery and the effect lasts for years.95-97

Graff-Radford et al described a case series of 10 patients developing cognitive complaints following RYGB. The cognitive impairment was attributed to bilateral posterior thalamic focal brain atrophy detected on volumetric MRI. The findings need to be verified by further studies.

**Spontaneous intracranial hypotension (SIH).** A case-control study has identified BS as a possible risk factor for spontaneous intracranial hypotension (SIH). In this study, 3.3% of the patients with SIH were found to have past history of BS compared with 0.8% of patients with un ruptured intracranial aneurysms. Effect of vitamin A and D deficiency on CSF absorption and possible spontaneous CSF leakage were the likely given explanation.

**Myelopathy/Myeloneuropathy.** Posterolateral myelopathy is one of the common and potentially disabling CNS complications of BS. Myelopathy may be associated with peripheral neuropathy resulting in a picture of myeloneuropathy. Myelopathy involves mostly the posterior columns with dorsal root ganglia. The onset is usually several years after the surgery and clinical manifestations include loss of proprioception, vibration, gait ataxia, hyperreflexia and Babinski sign. Sphincter dysfunction and limb weakness may also be seen. Involvement of the peripheral nerves can give glove and stocking pattern of sensory change. The myelopathy is mostly attributed to vitamin B12 deficiency after gastric bypass surgery; however, copper deficiency is now another well-established cause of myelopathy.

Optic neuropathy can be seen along with myeloneuropathy in copper deficiency. Folate deficiency is also a potential contributor and the clinical features are indistinguishable from vitamin B12 deficiency. Vitamin E (tocopherol) deficiency has also been identified as a cause of treatable myelopathy. Myelopathy involves mostly the posterior columns with dorsal root ganglia. The onset is usually several years after the surgery and clinical manifestations include loss of proprioception, vibration, gait ataxia, hyperreflexia and Babinski sign. Sphincter dysfunction and limb weakness may also be seen. Involvement of the peripheral nerves can give glove and stocking pattern of sensory change.

**Diagnosis and treatment of these common complications are outlined in Table 3.**

**Optic neuropathy.** Bariatric procedures associated with gastrointestinal malabsorption of vitamins and microelements may constitute a risk factor for nutritional optic neuropathy (NON). The NON results either from complete lack or insufficient dietary supply of nutrients needed for normal functioning of nerve fibers. Unilateral or bilateral optic neuropathy has been described after gastric bypass surgery associated with vitamin B12, copper, as well as vitamin A deficiency. A case of dermatitis and optic neuropathy due to zinc deficiency following BS has also been reported. The optic neuropathy can manifest slowly or acutely and can occur several years after BS. The pathogenesis is likely related to demyelination, however, the recovery may be incomplete and the blindness may be permanent.

In conclusion, With increasing obesity and increasing use of BS, it is likely that the neurologists and other healthcare professionals might encounter more neurological complications of these procedures in future. Patients, surgeons, internal medicine physicians, and neurologist need to be aware of these potential complications and should recognize that time to diagnosis and treatment matters. Early diagnosis and timely management may improve and possibly reverse the neurological deficit completely. Fortunately, many of these complications are potentially preventable. Lack of adherence to the postoperative nutritional replacement is still a significant issue. We strongly recommend the preoperative nutritional as well as psychological assessment of patients undergoing BS to prevent many of known complications. Appropriate screening, counselling and postoperative nutritional replacement should be the mainstay of management to avoid such catastrophic neurological complications. A routine multidisciplinary approach might help in reducing these complications as well. The review aims to raise awareness for the potentially permanent neurological complications and offers an overview of the most common CNS complications that can be encountered after BS. Neurological complications after endoscopic bariatric procedures, not described here separately need to be addressed as well and compared with other BS.

**Acknowledgment.** The authors gratefully acknowledge thank Dr. Fahd Sultan for his help in acquiring the original articles listed in the references.

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Stroke and seizure continue to be the major brunt of inpatient neurology care

An observation from teaching hospital

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ABSTRACT

Objectives: To assess the burden and describe the pattern of neurological disorders requiring admissions in a teaching hospital of Al Khobar.

Methods: This is a retrospective, cross sectional study, carried out in the Neurology Department of King Fahd Hospital of the University from January 2009 to December 2016. Neurological disorders were grouped as ischemic stroke, intracerebral hemorrhage, transient ischemic attack, cerebral venous sinus thrombosis, seizure disorders, central nervous system infection, multiple sclerosis, neuropathies, myopathies, headache, dementia and miscellaneous group. Data was entered and analyzed by Statistical Package for the Social Science (SPSS) version 22.0 (IBM Corp., Armonk, NY, USA).

Results: The records of 1,317 patients admitted under Neurology Service were analyzed. Out of that, 740 (56.2%) were male and 577 (43.8%) were female. Mean age was 46.9±24 years (mean±standard deviation). Ischemic stroke was the most common diagnosis (32%) followed by seizures (20%). Multiple sclerosis accounted for around 8% and central nervous system infections 5% of neurological admission.

Conclusion: Ischemic stroke was found to be the most common etiology for hospitalization in our study. The results of our study are similar to previous literature. An urgent need to control major risk factors such as diabetes and hypertension is warranted to minimize the burden of stroke.

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Neurological disorders (ND) represent a major burden of disease globally, and the spectrum ranges from non-communicable disorders such as cerebrovascular disease and neurodegenerative disorders to central nervous system (CNS) infections. The pattern of neurological admissions varies amongst different regions of the world, and depends on many factors, including the regional burden of disease. The spectrum of medical diseases in developing countries is different from that of developed countries due to multiple reasons. In a recent study, death was recorded in 19% of adults hospitalized with ND and disability in 53.6% of the survivors. In a one year retrospective survey from a tropical African hospital, ND constituted 24.2% of all medical conditions and stroke accounted for 42.1% of all cases.

A study from Nigeria found stroke and CNS infections as the most prevalent ND. One more study from Nigeria describing the profile of neurological admissions also found stroke and CNS infections as the most common reasons for admission. A retrospective study from tertiary care center in Ghana concluded that almost one in 3 patients admitted with ND died and most of them were attributed to non-communicable disorders.

One study from Saudi Arabia (SA) focusing on common diseases in hospitalized patients found cardiovascular system as the most commonly affected system (19.9%) followed by respiratory (14.5%). Cerebrovascular disease was found in only 2.0% of patients in this study.

The global burden of ND is approximately 20%, the majority being in the developing countries and still a significant portion is managed by non-neurologist physicians. In a community based survey from the Eastern province of SA, the reported crude prevalence of ND was 131/1000 population. Despite the fact that ND are projected to escalate worldwide in the coming decades; there is a paucity of published data on the burden, spectrum and outcomes of neurological admissions. There is a need to carry out research work in this field to know about the pattern of ND in hospitalized patients of SA, so more specialized centers can be established to deal with the diseases accordingly.

**Methods.** This is a retrospective, observational study, carried out in the Neurology Department of King Fahd Hospital of the University (KFHU). The KFHU is a 500-bedded tertiary care teaching and referral hospital. It has an established neurology team of residents, specialist and consultants providing round the clock service. Patients are admitted either through emergency or out-patient departments. The major source of admission is the Emergency Department. The department of neurology has separate specialty clinics for epilepsy, stroke, multiple sclerosis, dementia and neuromuscular disorders along with general neurology. These clinics are headed by consultants specialized in these fields. Acute ischemic stroke (IS) treatments as thrombolysis and neurovascular intervention are also provided at the center by a neurovascular team. A review of medical records of the patients admitted to KFHU over a period of 8 years (from January 2009 to December 2016) was performed after retrieving the data through the electronic data bank system. The study was approved by the institutional ethical committee. The records are maintained according to ICD-9 coding system in the electronic database system of the hospital. The medical records of all patients admitted under neurology service over the study period were reviewed. Patients found to have diseases requiring neurosurgery services care as cerebral neoplasms, compressive myelopathy, and subarachnoid hemorrhage were excluded from the current study. A structured form was used to collect the required information including demographic data as age, gender and nationality. Neurological disorders were grouped as IS, intracerebral hemorrhage (ICH), transient ischemic attack (TIA), cerebral venous sinus thrombosis (CVST), seizure disorders, CNS infection, multiple sclerosis (MS), neuropathies such as Guillain Barre Syndrome (GBS), chronic inflammatory demyelinating polyneuropathy (CIDP), diabetic and nutritional neuropathies, myopathies, headache, dementia, demyelinating diseases other than multiple sclerosis and miscellaneous group. Less common diseases such as motor neuron disease, radiculopathy, nonspecific encephalopathies and undiagnosed cases were included in miscellaneous group. Ischemic stroke, TIA, ICH and CVST were altogether considered as cerebrovascular disorders (CVD). Demographic characteristics as age, gender and nationality were recorded. Associated comorbidities such as hypertension, diabetes mellitus and ischemic heart disease were also recorded.

Relevant descriptive statistics, frequency and percentage were computed for neurological diagnoses and associated co morbidities such as diabetes mellitus, hypertension and ischemic heart disease. Data was expressed as mean ± standard deviation (SD) for age.
and length of stay. Data was entered and analyzed by Statistical Package for the Social Science (SPSS) version 22.0 (IBM Corp., Armonk, NY, USA). At 95% CI, p-value <0.05 was considered significant.

**Results.** A total of 89,573 patients were admitted in the hospital over the study period. A total of 1,317 (1.47%) patients were admitted under neurology department compared with 10,849 (12.11%) admitted under internal medicine. Neurology contributed to 8.07% of total patients admitted under medicine and all major subspecialties (neurology, cardiology, nephrology and gastroenterology) altogether. Summary of total admissions along with number and percentages of admission under internal medicine and other major subspecialties are described in Table 1. Percentage wise distribution of patients under different specialties in relation to medicine is shown in Figure 1. The burden of inpatients services shared by department of neurology and cardiology has increased over the past four years. The records of 1,317 patients admitted under neurology service were included in the study. Males were 740 (56.2%) and females 577 (43.8%) with M:F ratio of 1.2:1. Saudi patients were 996 (75.6%) while non Saudis were 321 (24.4%). Mean age was 46.9±24 years (mean±SD). Mean length of stay was 16.8±52.7 days (mean±SD). Hypertension was the most commonly identified associated comorbidity (44%), followed by diabetes mellitus (35%) and ischemic heart disease (8.8%). Among the ND requiring admission, CVD was the leading cause. Ischemic stroke (IS), TIA, ICH, and CVST included in CVD accounted for 41.6% of all admissions. In CVD group, IS was found in 75.5%, TIA 12.5%, ICH 9.4% and CVST 2.3%. Overall, IS was the most common reason for admission followed by seizure disorder, multiple sclerosis, neuropathies and CNS infections in decreasing frequency. Guillain Barre’ Syndrome was the reason for admission in 2.35% and CIDP 2%. Details are summarized in Figure 2. Death was observed in 86 (6.5%) patients during hospital stay. As it was a retrospective study, it was difficult to verify the exact cause of mortality. Demographic characteristics of major ND as mean age±SD, gender distribution and associated comorbidities are shown in Table 2.

**Discussion.** Majority of the patients presented after the age of 40 years with mean age of 46.9±24 years. This is similar to a hospital based study from Bangladesh but lower compared with studies from Nigeria. No significant difference in gender distribution was identified in the study overall. However, there was significant male preponderance in IS, ICH, TIA and CNS infections while females preponderance in MS and CVST. The percentage of inpatients admission under neurology service was 8.07% taking medicine and other major subspecialties altogether. In a study from SA, analyzing 5,594 admitted patients with

### Table 1 - Total admissions in hospital along with number and percentages of admission under neurology and other medicine services.

<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurology n (%)</td>
<td>108 (0.95)</td>
<td>92 (0.89)</td>
<td>70 (0.70)</td>
<td>78 (0.71)</td>
<td>202 (1.8)</td>
<td>200 (1.77)</td>
<td>287 (2.34)</td>
<td>280 (2.26)</td>
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<td>Medicine n (%)</td>
<td>1398 (12.3)</td>
<td>1242 (12.0)</td>
<td>1317 (13.2)</td>
<td>1295 (11.8)</td>
<td>1450 (12.8)</td>
<td>1489 (13.24)</td>
<td>1514 (12.38)</td>
<td>1144 (9.24)</td>
</tr>
<tr>
<td>Nephrology n (%)</td>
<td>228 (2.0)</td>
<td>147 (1.42)</td>
<td>161 (1.62)</td>
<td>235 (2.14)</td>
<td>155 (1.37)</td>
<td>157 (1.39)</td>
<td>163 (1.33)</td>
<td>211 (1.70)</td>
</tr>
<tr>
<td>Cardiology n (%)</td>
<td>99 (0.87)</td>
<td>88 (0.85)</td>
<td>81 (0.81)</td>
<td>170 (1.55)</td>
<td>224 (1.99)</td>
<td>175 (1.55)</td>
<td>389 (3.18)</td>
<td>777 (6.28)</td>
</tr>
<tr>
<td>Gastroenterology n (%)</td>
<td>101 (0.8)</td>
<td>67 (0.65)</td>
<td>23 (0.23)</td>
<td>58 (0.53)</td>
<td>51 (0.45)</td>
<td>122 (1.08)</td>
<td>169 (1.38)</td>
<td>105 (0.84)</td>
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<tr>
<td>Total admission in hospital</td>
<td>11325</td>
<td>10291</td>
<td>9923</td>
<td>10398</td>
<td>11256</td>
<td>11240</td>
<td>12229</td>
<td>12371</td>
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</table>

### Table 2 - Demographic characteristics of major neurological disorders.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Age (mean±SD)</th>
<th>Male</th>
<th>Female</th>
<th>Diabetes (%)</th>
<th>Hypertension (%)</th>
<th>IHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke</td>
<td>59.1±16.3</td>
<td>(65.2)</td>
<td>(34.7)</td>
<td>(60.8)</td>
<td>(74)</td>
<td>(16.6)</td>
</tr>
<tr>
<td>ICH</td>
<td>55.4±17.6</td>
<td>(67.3)</td>
<td>(32.9)</td>
<td>(28.8)</td>
<td>(73)</td>
<td>(3.8)</td>
</tr>
<tr>
<td>TIA</td>
<td>52.2±14.2</td>
<td>(73.9)</td>
<td>(26.0)</td>
<td>(40.5)</td>
<td>(60.8)</td>
<td>(14.4)</td>
</tr>
<tr>
<td>CVST</td>
<td>32.3±10.1</td>
<td>(31)</td>
<td>(69)</td>
<td>(7.7)</td>
<td>(46)</td>
<td>-</td>
</tr>
<tr>
<td>Seizures</td>
<td>36.8±19.7</td>
<td>(49)</td>
<td>(51)</td>
<td>(20)</td>
<td>(23)</td>
<td>(6.7)</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>28.9±8.6</td>
<td>(32)</td>
<td>(68)</td>
<td>(4.8)</td>
<td>(3.8)</td>
<td>-</td>
</tr>
<tr>
<td>CNS infection</td>
<td>37.2±14.3</td>
<td>(62.5)</td>
<td>(37.5)</td>
<td>(28)</td>
<td>(15)</td>
<td>(1)</td>
</tr>
</tbody>
</table>

ICH - intracerebral hemorrhage, TIA - transient ischemic attack, CVST - cerebral venous sinus thrombosis, CNS - central nervous system, IHD - ischemic heart disease
medical disease according to systemic involvement, CNS involvement was identified in nearly 5% of cases and cerebrovascular events were ranked tenth among the sixteen most common diagnoses in hospitalized patients. The estimated burden of ND in our study was lower compared with other hospital based studies, reporting a burden range of 21-24%. However, an increase in absolute number and percentage of patients with neurological diseases has been observed over the past 4 years. Hypertension was the most commonly associated comorbidity in our cohort. The prevalence of hypertension in KSA is on rising side and affects more than one fourth of adult Saudi population. In a community based study, the reported prevalence was 28.6% for males and 23.9% for females. Diabetes mellitus was found in significant number (35.2%) of patients. An approximately 10 fold increase in diabetes has been observed in the past 3 eras in SA.

Ischemic stroke was the most common reason for hospitalization as identified in other studies describing the pattern of in-patient ND. The percentage in our study was less as compared with hospital based registries from Nigeria as reported by Ekenze et al (64.9%), Eze et al (62%) and Philip-Ephrahim et al (42.1%), but comparable to a report by Gajurel et al (36%) from Nepal. Significantly higher prevalence of hypertension (74%) and diabetes mellitus (60%) in these patients is of real concern and emphasizes the need for implementation of adequate preventive measures to control these modifiable risk factors. Seizure was the second most commonly identified diagnosis. Seizure was also identified as the second most common cause of referral to neurologist after stroke by Chowdhury et al, and Gajurel et al. The reported prevalence rate (6.45/1000) of active epilepsy in Saudi nationals is not different from other developed and developing countries. Epilepsy is one of the chronic and common ND having significant physical, social and economic implications on the patients, care givers and health care system. According to a recent study describing the epilepsy services in SA, there is a real shortage of epileptologist and epilepsy

Figure 1 - Yearly percentage distribution of patients under different specialties in relation to medicine

Figure 2 - Neurological disorders identified in patients admitted under neurology
monitoring units (EMU), especially in the northern and southern regions of KSA. Multiple sclerosis was the leading cause of hospitalization following IS and seizures. The change in epidemiology of MS has been observed worldwide. Although, the Arabian Gulf Region is located in a low risk zone, an increase in the incidence has been reported in recent years. Change in life style, relatively increase proportion of younger population, vitamin D deficiency and consanguineous marriages are considered as contributing factors. In one study from SA including 806 neurology patients, MS was diagnosed in 16 patients (2.35%). The mean age in our study was similar to overall estimated age of 28.5 years described in a literature survey on MS epidemiology in the Middle East and North African countries. Central Nervous System infections were less frequent than reported by Ekenze et al (21.8%), The difference could be attributed to better infection preventive measures in KSA. As KSA faces a huge burden of pilgrims annually during Hajj, the Saudi Ministry of Health acts strictly to prevent infections hazards as meningococcal meningitis and other infections by an effective international partnership in the area of infection control and preventive medicines. A major limitation of our study is its retrospective nature causing difficulty in ascertaining the diagnosis in a few cases and identifying the reasons for mortality.

Patients with a wide spectrum of ND were admitted during the study period. Cerebrovascular diseases, seizure disorders and multiple sclerosis are the main ND requiring hospitalization. There is a need for further prospective epidemiological studies to estimate the real burden and assess the spectrum of ND in the kingdom. Separate neurovascular services and establishment of stroke center along with rehabilitation center are the real need to optimize the care of patients with stroke, the leading ND.

Acknowledgment. We are thankful to the administration and statistics department of King Fahd Hospital of the University for providing records of admitted patients.

References

Demographic and histopathological patterns of neuro-epithelial brain tumors in Eastern Province of Saudi Arabia

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ABSTRACT

Objectives: To review the demographic and pathological pattern of neuro-epithelial brain tumors in a tertiary referral center in the Eastern Province of Saudi Arabia and to compare the results of our study with other national and international studies.

Methods: This is a retrospective chart-review study of all patients with neuro-epithelial brain tumors referred and treated in our center between January 2010 and January 2015. The age, gender, tumor location, and histopathology were recorded.

Results: The total number of cases was 149 including 96 adult cases and 53 pediatric cases. 58% of cases were male, and 42% were female. The age group distribution showed 2 peaks; one in the first 5 years of life and the second was in the age range from 26-45 years old. Glioblastoma multiforme was the most common pathological type (32%), followed by medulloblastoma (13.3%). This study showed similar results to a previous study conducted in the Eastern Province in terms of age and gender distribution, but pathologically, the tumors diagnosed in our study were generally of a higher grading. When comparing our results to other international studies in nearby countries (Jordan and Egypt), we found similarities in pathological patterns and age distribution. However, when comparing our results to a western country (USA), we found considerable differences in the age group distribution.

Conclusion: Neuro-epithelial brain tumors in Saudi Arabia affect younger population according to our study compared to Western countries. These findings are similar to other studies from Middle Eastern countries. In addition, our study showed a significant increase in high grade gliomas in the Eastern Province compared to an old historical study. This increase should be interpreted cautiously due to possible selection errors, changes in pathological grading, and expertise.
The term “primary brain tumors” refers to a mixed group of neoplasms arising from different intracranial tissues with degrees of malignancy ranging from slow growing to aggressive types. Each type has its own biology, treatment, and prognosis. These tumors are unique and different in their behavior and even “benign” tumors can be catastrophic due to their location, their ability to infiltrate locally, and the potential to transform into malignancy.1 Primary central nervous system (CNS) tumors are divided into the following major groupings: tumors of neuro-epithelial tissue (including gliomas, medulloblastoma, and others), tumors of meninges (including meningiomas), germ cell tumors, tumors of nerve sheath (like vestibular schwannomas), and tumors arising from the sellar region (including pituitary adenomas).2 The World Health Organization (WHO) classification for CNS tumors, developed in 1979 and revised in 1999, 2007, and 2016 has been universally adopted in grouping CNS tumors according to their behavior and aggressiveness.3-4 Primary CNS tumors are a rare occurrence accounting for only 2% of all cancers in adults, but account for approximately 20% of cancers in children.5 Neuro-epithelial brain tumors accounts for almost 80-90% of primary brain malignancies and their occurrence and pathological patterns are used worldwide to analyze the incidence and epidemiology of primary brain cancer in different countries.6 The aim of our study is to review the demographic and pathological pattern of neuro-epithelial brain tumors in our center which is a tertiary referral center for the whole of the Eastern Province and compare our results with other national and international studies.

Methods. King Fahad specialist hospital in Dammam has accommodated the Oncology Center for the whole of Eastern province since 2007. The neuro-oncology multidisciplinary tumor board (MDT) was established in 2009 to review and discuss all neuro-oncological cases referred or treated in our hospital. All cases of primary brain tumors including adult and pediatric are discussed in the meeting for future management. The list of cases discussed in the MDT is saved in a spreadsheet for quality assurance and for future research.

We retrospectively reviewed all cases of neuro-epithelial tumors from our neuro-oncology MDT list between January 2010 and January 2015 (5 years). The IRB approval was obtained for this study. Age, gender, tumor location, imaging and histopathology diagnosis were recorded for our analysis. For grading and pathological diagnosis, we used the 2007 edition of WHO classification for CNS tumors.3

Inclusion and exclusion criteria. The study included all cases of neuro-epithelial tumor with pathological confirmation. We also included certain neuro-epithelial tumors, which can be diagnosed based on radiology diagnosis such as diffuse intrinsic brain stem glioma and optic pathway glioma. All other CNS tumors like metastasis, meningiomas, and lymphomas were excluded.

Statistical analysis. Statistical analysis was performed by using the Statistical Package for Social Science version 12 (SSPS Inc., Chicago, IL, USA). The percentage was calculated in the presence and absence group by

**Figure 1** - Shows the age grouping in percentage for all cases of the study.

Disclosure. Authors have no conflict of interests, and the work was not supported or funded by any drug company.
Table 1 - Pathological types for all cases of the study.

<table>
<thead>
<tr>
<th>Histology type</th>
<th>KFSH-D (%)</th>
</tr>
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<tbody>
<tr>
<td>Pilocytic Astrocytoma (WHO 1) (infra-tentorial)</td>
<td>11 (7.3)</td>
</tr>
<tr>
<td>Pilocytic Astrocytoma (WHO 1) (Optic pathway glioma)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Diffuse Astrocytoma (WHO 11)</td>
<td>7 (4.6)</td>
</tr>
<tr>
<td>Anaplastic Astrocytoma (WHO 111)</td>
<td>13 (8.7)</td>
</tr>
<tr>
<td>Oligodendroglioma (WHO 11)</td>
<td>4 (2.7)</td>
</tr>
<tr>
<td>Anaplastic oligodendroglioma (WHO 111)</td>
<td>9 (6)</td>
</tr>
<tr>
<td>Mixed glioma (WHO 11)</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>Mixed glioma (WHO111)</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>Diffuse brain stem glioma</td>
<td>9 (6)</td>
</tr>
<tr>
<td>GBM (WHO IV)</td>
<td>48 (32)</td>
</tr>
<tr>
<td>Gliosarcoma (WHO IV)</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>Ependymoma (WHO 11 and WHO 111)</td>
<td>11 (7.3)</td>
</tr>
<tr>
<td>PNET/MB (WHO IV) (Infra-tentorial)</td>
<td>16 (10.7)</td>
</tr>
<tr>
<td>PNET (WHO IV) (supra-tentorial)</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>Pineoblastoma I tumors (WHO IV)</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>Choroid plexus papilloma/ carcinoma</td>
<td>3 (2)</td>
</tr>
<tr>
<td>PXA (WHO 11 and 111)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Central Neurocytoma (WHO 11)</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>149 (100)</strong></td>
</tr>
</tbody>
</table>

GBM - Glioblastoma multiforme, PNET - Primitive Neuroectodermal Tumor, MB - Medulloblastoma, PXA - Pleomorphic Xanthoastrocytoma

Pearson's Chi-square test. The limit of the statistical significance was set at $p<0.05$.

Results. The total number of cases was 149. Pathological diagnosis was available for 140 patients, and the other 9 cases were treated on the basis of their imaging (cases of diffuse brain stem gliomas and optic pathway gliomas). The percentage of male and female in our study were: 58% male versus 42% female. The percentage of adult and pediatric cases (16 years and below) were: 64.4% adult and 35.6% pediatric. Figure 1 shows the age grouping in percentage for all cases. We have 2 peaks; one in the first 5 years of life and second in the age group (26-45 years). The locations of the tumors were 69% supra-tentorial versus 31% infra-tentorial.

The pathological types for all of our cases are summarized in Table 1. As shown from the table: Glioblastoma Multiform (WHO IV) cases were the highest (32%), Primitive Neuroectodermal tumors (PNET)/ Medulloblastoma (WHO IV) were (12.3%), Pilocytic Astrocytoma (WHO I) 9.3%, Anaplastic Astrocytoma (WHO III) 8.7%, Oligodendroglioma (WHO II, III) 8.6%, Ependymoma (WHO II, III) 7.3%, Diffuse brain stem glioma 6%, Diffuse Astrocytoma (WHO II) 4.6%, and the remaining were less than 3 % each.

We have 53 cases of pediatric tumors. The PNET including Medulloblastoma were the highest among children 28.3%, High grade gliomas were 15%, pilocytic astrocytoma including the optic pathway gliomas were 16.8%, ependymoma 15%, and diffuse brain stem gliomas were 11.3%, and the remaining were less than 5%.

In the adult group: GBM was the highest 43.7%, followed by anaplastic astrocytoma 9.3%, oligodendroglioma 9.3%, PNET 6.2%, pilocytic astrocytoma 5.2 %, diffuse astrocytoma was 5.2 % and mixed gliomas 5.2%.
Table 2 - Shows the pathological types of the KFUH study.\textsuperscript{14}

<table>
<thead>
<tr>
<th>Pathological Type</th>
<th>Cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low grade glioma (pilocytic WHO 1) and diffuse astrocytoma (WHO 11)</td>
<td>40</td>
<td>(28)</td>
</tr>
<tr>
<td>Anaplastic Astrocytoma (WHO 111)</td>
<td>18</td>
<td>(12.5)</td>
</tr>
<tr>
<td>Oligodendroglioma (WHO 11)</td>
<td>8</td>
<td>(6)</td>
</tr>
<tr>
<td>Anaplastic oligodendroglioma</td>
<td>1</td>
<td>(0.7)</td>
</tr>
<tr>
<td>Mixed glioma (WHO 11)</td>
<td>3</td>
<td>(2.1)</td>
</tr>
<tr>
<td>GBM (WHO IV)</td>
<td>30</td>
<td>(21)</td>
</tr>
<tr>
<td>Ependymoma (WHO 1 and 11)</td>
<td>7</td>
<td>(4.9)</td>
</tr>
<tr>
<td>PNET (WHO IV)</td>
<td>28</td>
<td>(19.5)</td>
</tr>
<tr>
<td>Choroid plexus papilloma/ carcinoma</td>
<td>4</td>
<td>(2.8)</td>
</tr>
<tr>
<td>Pineal tumors</td>
<td>3</td>
<td>(1)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>142</td>
<td>(100)</td>
</tr>
</tbody>
</table>

GBM - Glioblastoma multiforme, PNET - Primitive Neuroectodermal Tumor, MB - Medulloblastoma

Discussion. The incidence of brain cancer in Saudi Arabia is relatively low according to the Saudi Cancer Registry (cancer incidence report 2010).\textsuperscript{7} Brain cancer forms 3.2% of all cancer in males in Saudi Arabia, and 2% in females. The age standardized incidence rate per 100,000 populations was 1.9 in males and 1.4 in females according to the same report.\textsuperscript{7} This incidence rate is considered the lowest in comparison to other countries (Figure 2).\textsuperscript{8}

The pathological patterns of brain cancer were not published in the Saudi cancer registry since it constitutes a small percentage of all cancer cases.\textsuperscript{7} In addition, only cases with pathological confirmations of high-grade nature were included in the registry. Therefore, some brain tumors such as low-grade glioma, diffuse brain stem gliomas, and optic pathways gliomas which are diagnosed and treated based on brain imaging only, were not included in the cancer registry. Some of these tumors are considered aggressive and they are treated with chemotherapy and radiation therapy.\textsuperscript{9,10}

Comparison to national studies. We have found few studies in the literature that have reported the pathological patterns of brain tumors in Saudi Arabia. Most of them were small, and they reported all types of brain tumors including meningioma, pituitary adenomas, brain metastasis…etc. The percentage of neuro-epithelial brain tumors in these studies were quite small to make any statistical comparisons\textsuperscript{11-13}

One study from King Fahad University Hospital (KFUH) -Al-Khobar in the Eastern province of Saudi Arabia had a larger sample with a sizable percentage of neuro-epithelial brain tumors. The study included all CNS tumors according to the WHO classifications (1979 edition).\textsuperscript{14} The authors retrospectively reviewed all CNS tumor cases treated in all Eastern Province hospitals between January 1982 and January 1991 (9 years). A total of 142 cases of neuro-epithelial tumors...
were reported (Table 2). When comparing their results to our study, we found similarities in the gender and age group distributions; male 61.5%, female 38.5%, adult 58% and pediatrics 42% (in KFUH study). On the other hand, when comparing the pathological patterns between both studies, there were significant differences. We found increase in high-grade gliomas cases in our study (81 cases) compared to KFUH study (49 cases). This difference is significant ($p<0.05$). Similarly, when comparing all cases of low grade gliomas in both studies (28 cases in our study versus 51 cases in KFUH study) the difference is also significant. The differences of other types of neuro-epithelial tumors are not significant.

The increase in high grade gliomas in our study in comparison to the KFUH study should be cautiously interpreted. It could be attributed to a selection bias since the historical (KFUH) study included cases from 4 major hospitals in the region while our study included only cases treated in or referred to our center for adjuvant therapy (chemotherapy or radiotherapy). The differences in pathological grading and expertise between the 2 studies might also affect the results of the pathological diagnosis. In addition, environmental factors could also be considered. In our view, more collaborative and prospective studies are needed to investigate these results further.

**Comparison to international studies.** The Middle East Cancer Consortium (MECC) previously published a large report on the incidence of cancers and their pathological patterns in several Middle Eastern countries. It also reported the incidence and pathologies of these tumors in the United State for comparison purposes. The report covered the period between 1996 and 2001. We compared our results to 2 Middle Eastern countries (Egypt and Jordan) in addition to the US results. We found no major differences in the pathological patterns of neuro-epithelial brain tumors between our results and the results of the three counties (Figure 3).

When comparing the age group between our study and the MECC report, we found that neuro-epithelial tumors in our study are more common in younger patients (41.6% in patients below 20 years and 39.5% in patients between 20 and 49 years) and less common in older patients (16.1% between 50 and 69 years and only 2.6% above 70). Similar results were observed in the other 2 Middle Eastern countries. However, when compared to the USA study, the age groups affected by brain cancer in the US study were older, only 14% below 20 years, 28% (20-49 years) 31% (50-69 years) and 27% above 70 (Figure 4). This difference is more often linked to the differences in population age structure, rather than underlying incidence rates.

Despite the small size of our sample, our results provide useful information on the pathological and the demographic patterns of neuro-epithelial primary brain tumors in the Eastern Province region and possibly in the whole of Saudi Arabia.

**Acknowledgment.** We would like to thank Mrs. Nada Alfarhan for her kind help in the English editing of this paper.

**References**

Comparison of 2 methods of neuropathic pain assessment in carpal tunnel syndrome and hand functions

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ABSTRACT

Objectives: To compare the effectiveness of the Leeds Assessment of Neuropathic Symptoms and Signs Scale (LANSS) to the painDETECT questionnaire (PD-Q) in Carpal Tunnel Syndrome (CTS), and determine if there are any differences between hand related functions in the 2 questionnaires.

Methods: This prospective clinical trial was conducted from April to July 2014. Ninety patients with a positive Tinel or Phalen sign were recruited. Hands were evaluated by electromyography and grouped according to mild, moderate or severe involvement. Neuropathic pain was analysed by the LANSS and the PD-Q; hand functions were evaluated by the Duruöz Hand Index (DHI), Semmes Weinstein monofilaments and grip strength.

Results: Electromyographic findings revealed 32.9% of hands had mild, 61.8% had moderate and 5.3% had severe CTS. There was a correlation between the LANSS scores and the Visual Analogue Scale (VAS) pain, while the PD-Q scores were correlated with the VAS pain, DHI and Semmes Weinstein Monofilaments (SWM). Comparison of the hand related parameters of the questionnaires showed there was a statistically significant difference between the 2 groups with respect to the DHI and SWM tests in the PD-Q. However, there was no difference in the LANSS.

Conclusion: Although there was a significant correlation between the LANSS and PD-Q scores, the PD-Q scores revealed better correlation coefficients in VAS pain, DHI scores and SWM tests. In conclusion, the PD-Q seems to be better than the LANSS both in neuropathic pain and in detecting functions related to hand abilities.

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Carpal Tunnel Syndrome (CTS) is an entrapment neuropathy. The estimated prevalence is 5%-16% in the general population, including all adults globally.\(^1\)\(^2\) It occurs due to the compression of the median nerve beneath the transverse carpal ligament, and the increased pressure within the tunnel results in mechanical compression and/or local ischemia in the nerve.\(^3\) Primary features of CTS include pain in the hand, unpleasant tingling and numbness, reduction of the grip strength and problems in hand functions. In CTS, in addition to soft tissue and other musculoskeletal disorders, peripheral nerve lesions and nociceptive mechanisms of musculoskeletal problems can also be caused by pain.\(^4\)

Clinical tests, such as the Tinel sign and Phalen test, are helpful in diagnosing CTS.\(^5\) However, the diagnosis becomes definite by using nerve conduction studies where prolonged motor and sensory latencies, as well as reduced sensory and motor conduction velocities, are determined.\(^6\) In clinical evaluations of CTS, sensibility tests such as tuning forks, vibration tests, Semmes-Weinstein monofilaments and two-point discrimination tests can be used.\(^7\)\(^8\)

Peripheral neuropathy is one of the common causes of CTS pain. It is more common in patients with diabetes mellitus, vitamin B12 deficiency and dysproteinemias.\(^9\) In our study, we aimed at detecting the neuropathic component of carpal tunnel syndrome. In the evaluation of neuropathic pain, different instruments can be used such as the Leeds Assessment of Neuropathic Symptoms and Signs Scale (LANSS), Douleur Neuropathique en 4 questions (DN4), the painDETECT questionnaire (PD-Q), the Neuropathic Pain Questionnaire, and others. The LANSS contains 5 items of symptoms and 2 items of clinical examination. PD-Q consists of 7 sensory descriptive items and 2 items related to spatial and temporal characteristics. It is one of the most frequently utilized scales.\(^10\) In this study, we aimed at comparing the efficacy of the LANSS and the PD-Q in CTS and their relationship with hand functions.

**Methods.** The study took place from 01-04-2014 to 25-07-2014. Two methods of neuropathic pain assessment (LANSS and PD-Q) were compared. Ninety-five patients suffering from numbness in their hands and with a positive Tinel or Phalen sign were selected, consecutively, among the patients who were admitted to Physical Medicine and Rehabilitation outpatient clinics at Ankara Education and Research Hospital, Ankara, Turkey. Out of that number, 18 patients were excluded due to cervical radiculopathy, rheumatologic disease, diabetes mellitus and a history of upper limb surgery. A total of 77 patients were included in the study.

The study was approved by the local medical ethics committee, and written informed consent was obtained from each candidate. This was in accordance with the Helsinki Declaration Principles. A Nerve Conduction study (NCS) was performed, using a Nihon-Kohden Neuropack M1 (Tokyo, Japan), by the same physiatrist who was blinded to the subjects’ identity and the clinical data. All studies were conducted at standard room temperature (25°C). The skin temperature of the hand was maintained at 32°C or above. The median compound muscle action potentials (CMAPs) were recorded over the abductor pollicis brevis muscle via median nerve stimulation and applied at 8 cm proximal to the active recording electrode. The onset latency and the baseline-to-peak amplitude of the CMAPs were measured. The median Sensory Nerve Action Potentials (SNAPs) were recorded antidromically with a bar electrode over the third digit and stimulated at 2 points located at 7 and 14 cm proximal to the active recording electrode. To test the transcarpal segment, the nerve was also stimulated at 2 points: at the Distal Wrist Crease (DWC) and 5 cm distal to the DWC in the palm. The latencies and the baseline-to-peak amplitudes of the median SNAPs were measured and the onset latency difference between the 2 points was calculated.

Carpal tunnel syndrome was diagnosed by a median SNAP peak latency of >3.7 ms, a SNAP peak latency longer in the proximal 7 cm segment than in the distal 7 cm segment, a SNAP amplitude <20 µV and a conduction block with a SNAP amplitude decrease of >50% with wrist stimulation compared to palm stimulation, a 5 cm transcarpal conduction time of >1.3 ms, a median CMAP distal latency of >4.2 ms, and a CMAP amplitude of <4.5 mV.\(^11\) According to the results of electrophysiological findings, 77 patients were diagnosed with mild, moderate, or severe CTS. The severity of pain in the hands was analyzed by a Visual Analogue Scale (VAS) from 0-10 cm. Neuropathic pain was evaluated by the LANSS and the PD-Q. The LANNS is a seven-item pain scale that consists of a grouped sensory description and sensory examination with a simple scoring system. The first part is based on

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**Disclosure.** Authors have no conflict of interests, and the work was not supported or funded by any drug company.
Table 1 - Minimum, maximum and mean±standard deviation of evaluation parameters.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>22</td>
<td>73,00</td>
<td>47.43±10.6</td>
</tr>
<tr>
<td>VAS pain</td>
<td>0.00</td>
<td>10</td>
<td>4.15±2.8</td>
</tr>
<tr>
<td>LANSS</td>
<td>0.00</td>
<td>25,00</td>
<td>16.57±6.5</td>
</tr>
<tr>
<td>PD-Q</td>
<td>1.0</td>
<td>30.00</td>
<td>16.70±6.07</td>
</tr>
<tr>
<td>Hand grip strength(kg)</td>
<td>9</td>
<td>43.3</td>
<td>23.63±7.8</td>
</tr>
<tr>
<td>DHI</td>
<td>0.00</td>
<td>72.00</td>
<td>23.36±17.6</td>
</tr>
<tr>
<td>SWF</td>
<td>2.83</td>
<td>4.56</td>
<td>3.49±0.5</td>
</tr>
</tbody>
</table>

VAS - Visual Analogue Scale, LANSS - Leeds Assessment of Neuropathic Symptoms and Signs Scale, PD-Q - painDETECT Questionnaire, DHI - Duruöz Hand Index, SWF - Semmes Weinstein Monofilaments, SD - Standard Deviation

Table 2 - VAS-pain scores of neuropathic pain positive and negative groups by LANSS and PDQ.

<table>
<thead>
<tr>
<th>VAS neuropathic pain</th>
<th>Negative</th>
<th>Positive</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Min- max</td>
<td>Mean±SD</td>
<td>Min- max</td>
<td>Mean±SD</td>
</tr>
<tr>
<td>LANSS</td>
<td>0-9</td>
<td>3.16±2.8</td>
<td>0-10</td>
</tr>
<tr>
<td>PD-Q</td>
<td>0-8</td>
<td>3.16±2.39</td>
<td>0-10</td>
</tr>
</tbody>
</table>

LANSS - Leeds Assessment of Neuropathic Symptoms and Signs Scale, PD-Q - painDETECT questionnaire, VAS - Visual Analogue Scale

5 questions that consist of the following: the presence of unpleasant skin sensations like pins and needles or prickling, color changes in the skin (red, mottled or pink), increased sensitivity of the skin to the touch and bursts of pain for no reason. In the second part, skin sensitivity is examined by comparing the painful area with the non-painful one for the presence of allodynia and an altered pin prick threshold. A score of less than 12 indicates that the pain is unlikely to be of neuropathic origin, whereas a score of 12 or more is likely to be neuropathic. The sensitivity and specificity of the LANNS questionnaire is 85% and 80% respectively.12

The painDETECT questionnaire is another neuropathic pain screening tool which was developed and validated in Germany for low back pain patients.13 We used the questionnaire with 9 items. Seven of the items were sensory descriptor related items and 2 of them were related to the spatial and temporal characteristics of the pain pattern. A score of ≤12 indicates that neuropathic pain is unlikely. A score between >12 and <19 indicates neuropathic pain is possible, and a score of ≥19 demonstrates that neuropathic pain is likely. The sensitivity and specificity of the PD-Q are 85% and 80% respectively.14 The PD-Q has been used to identify neuropathic pain in fibromyalgia, knee osteoarthritis, diabetic neuropathy and post-herpetic neuralgia.15-17

Turkish validity and reliability of both the LANSS and the PD-Q have been carried out.18,19

Hand functions of the patients were evaluated by the Duruöz Hand Index (DHI).20 The DHI is a self-report questionnaire which was developed to evaluate the capacity of carrying out manual functional activities in patients with rheumatoid arthritis. This scale is validated in scleroderma, hemiparesis, flexor tendon trauma and diabetic hands. It consists of 18 questions regarding manual tasks which are frequently carried out during daily activities. The patient was asked to evaluate the difficulty which he/she had in carrying out these tasks (from 0: no difficulty, to 4: nearly impossible); the total score ranges were between 0 and 90. The reliability and validity of the Turkish version of the DHI were proven in patients with stroke, diabetes mellitus, and hand flexor tendon injury.21-23

Hand grip strength was evaluated by the Jamar dynamometer. The patient sat on a chair with her/his shoulder in the neutral position, elbow at 90° and wrist at 0°. The second handle position was used in determining the grip strength. The average of 3 trials was recorded.24 Hand grip strength is necessary in daily activities such as carrying laundry, vacuuming, turning a door knob etc. It is a simple marker of muscle strength in upper extremities. Low grip strength in healthy adults predicts an increased risk of functional limitations and disability at a more advanced age. Muscle function reacts early to nutritional deprivation and hand grip strength becomes a popular marker of nutritional status.25

Cutaneous sensibility of the hands was assessed by Semmes-Weinstein Aesthesiometer monofilaments (SWM). The examiner first established an area of normal sensitivity in the patient’s hand, familiarized the patient with the filament (2.83) to be used, and then demonstrated it in the normal sensibility area. Then, with the patient’s eyes occluded, the examiner demonstrated the filament (2.83) on the median nerve innervation area. If the patient could not feel the touch of the 2.83 filament, the examiner tried with the 3.61, 4.31 and 6.65 filaments. Filament 2.83 represents normal sensation; 3.61 implies light touch diminution; 4.31 shows that protective sensation is decreased and 6.65 indicates loss of protective sensation.26

Statistical analyses. All statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS), version 15.0 for Windows. All numerical data are expressed as the mean±standard deviation. The comparisons between groups were performed by the Mann Whitney-U test. Correlations were analyzed using Spearman’s rank correlation coefficient. The significance threshold was set at 0.05.
Results. The study consisted of 77 patients (66 females, 11 males); the mean age of the patients was 47.93±10.6 years. Electromyographic findings revealed that 25 (32.9%) hands had mild CTS, 47 (61.8%) hands had moderate CTS and 4 (5.3%) hands had severe CTS. In the PD-Q evaluation, we found that 19 of the 77 hands fell between >12 and <19. These patients were excluded and we continued with 58 patients in the PD-Q group.

The demographic characteristics of the patients can be seen in Table 1. The distribution of the VAS pain scores between neuropathic pain positive and negative groups is shown in Table 2. There was a statistically significant difference in the VAS pain scores between neuropathic pain positive and negative groups in both the LANSS and the PD-Q evaluations, and the VAS pain scores were also found to be significantly higher in the neuropathic pain positive groups.

Correlations of the VAS, hand grip strength, Duruöz hand index score, SWF with LANSS and PD-Q can be seen in Table 3. While the evaluation parameters, except for age and hand grip strength, correlated significantly with the PD-Q and only the VAS had significant correlation with the LANSS.

In the comparison of hand grip strength, DHI scores, and SWF scores between neuropathic pain positive and negative groups in both questionnaires, we found that all parameters in the PD-Q were significantly different between the neuropathic pain positive and the negative groups, while no difference existed between the neuropathic pain positive and the negative groups of the LANSS (Table 4).

Discussion. Carpal tunnel syndrome is an entrapment neuropathy which is a commonly encountered peripheral nerve lesion of the median nerve. It can cause neuropathic pain and functional decrease in hand functions. Patients have a burning sensation and decreased function in the first three fingers, which are very important in daily activities.27

We evaluated neuropathic pain by the LANSS and the PD-Q and investigated if there was a difference between the questionnaires in determining neuropathic pain of the hands. We also examined if there was a difference between the 2 questionnaires on hand functions in terms of hand grip strength, cutaneous sensibility and DHI evaluations. An important limitation of our study was the limited number of the patients.

It was stated, in a systematic review of Mathieson et al28 that of all the neuropathic pain screening questionnaires, none were found to be satisfactory. Although these questionnaires provided an indication of the presence of neuropathic pain, they could not replace a clinical assessment. Also, in Tampin et al29 study, neuropathic pain was examined in patients with neck and upper limb pain by the PD-Q and the LANSS. The authors indicated that both of the questionnaires had limited diagnostic accuracy.

The main complaint by our patients was about hand pain of a neuropathic nature. We evaluated the pain status of the patients with the VAS 0-10 scale and found that both of the questionnaires had a significant correlation with the VAS scores and there was also a statistically significant difference between neuropathic pain positive and negative groups in both questionnaires (LANSS p=0.002; PD-Q p=0.000). Similar to our findings, Sonohata et al10 found significant differences in the pain scores between the patients with and without neuropathic pain (p<0.01).
In our study, we found a significant difference between neuropathic pain positive and negative groups in the VAS of the LANSS and the PD-Q. In clinical evaluations, we compared the hand grip strength, DHI, and SWF scores of neuropathic pain positive and negative groups of both questionnaires. In comparisons of hand related evaluations, we found a statistically significant difference between neuropathic pain positive and negative groups in all parameters of PD-Q. However, we found no significant difference between the groups in the LANSS. In hand related evaluations, the PD-Q had significant correlations. We found only 2 studies about neuropathic pain and hand related evaluations. In two studies by Sonohata et al PD-Q patients were grouped as "unlikely", "possible" and "likely neuropathic pain" and they did not find any statistically significant difference between the groups in terms of pain, hand grip strength and SWF tests.10 There are limitations to our study. The study was conducted in patients with mild, moderate and severe CTS, but the number of severe CTS patients was inadequate. The other limitation was the use of the Turkish versions of the tests. Our findings may not be directly generalizable over the versions in other countries.

In conclusion, in this study, although there was a significant correlation between the LANSS and the PD-Q scores, we found that neuropathic pain was positive in 77 hands of LANSS and 58 hands of PD-Q assessments. When the hand functions and hand sensory evaluation results are considered, the PD-Q seems to be more effective than the LANNS in evaluation of neuropathic pain in patients with CTS.

References


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**Statistics**

Excerpts from the Uniform Requirements for Manuscripts Submitted to Biomedical Journals updated November 2003. Available from [www.icmje.org](http://www.icmje.org)

Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Avoid relying solely on statistical hypothesis testing, such as the use of *P* values, which fails to convey important information about effect size. References for the design of the study and statistical methods should be to standard works when possible (with pages stated). Define statistical terms, abbreviations, and most symbols. Specify the computer software used.
APOE Gene polymorphism among Jordanian Alzheimer’s patients with relation to lipid profile

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ABSTRACT

The objectives: To investigate the frequencies of the apolipoprotein E (APOE) alleles and genotypes and study their relationship with the lipid profile in Jordanian patients with late-onset Alzheimer's disease (AD).

Methods: This case-control study was carried out on 71 Jordanian individuals: 38 patients with late-onset AD (age ≥65 years) and 33 age-matched healthy controls. All participants were recruited from senior homes and Jordan University Hospital, Amman, Jordan between January 2010 and December 2013. Each sample was examined for APOE’s 3 major isoforms (ε2, ε3, ε4) using the polymerase chain reaction technique (PCR) followed by the sequencing technique. In addition, samples were screened for lipid profiles (total cholesterol (TC), high-density lipoprotein (HDL), lower-density lipoprotein (LDL), and triglyceride (TG) levels.

Results: The ε3/ε4 genotype and ε4 allele prevalence were higher in AD patients compared to healthy controls (26.3% vs. 3.0%, p=0.03 and 15.8% vs. 4.5%, p=0.03; respectively). In the AD group, the ε2 carriers showed the lowest levels of total and LDL cholesterol, and the ε4 carriers showed the highest levels of total and LDL cholesterol, although the difference was not statistically significant (p>0.05).

Conclusion: APOE-ε4 frequency was almost 4 times higher in the AD group compared to the control group, and this difference was statistically significant. A trend that was observed in the AD group regarding the lipid profile and ε2 and ε4 carriers requires further investigation using a larger sample size.

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Alzheimer’s disease (AD) is a complex neurodegenerative disorder that is progressive in nature and has poor prognosis. Diagnosis of AD is made with certainty only by brain biopsy or autopsy. Today, the diagnosis of AD is possible by conducting a thorough medical history, mental status testing, and physical and neurological exams and tests (such as blood tests and brain imaging) to rule out other causes of dementia-like symptoms. The incidence of AD in Jordan has not been reported yet. It has been estimated that 0.2-0.3% of Jordanians could be clinically classified as having AD. Although the etiology of AD has yet to be elucidated, it is known to be a multifactorial disorder. Most likely, the development of the disease is a result of the interaction of several susceptible genes and environmental risk factors. Therefore, it is difficult to pinpoint a single gene polymorphism in the pathogenesis of AD. However, apolipoprotein E (APOE) gene polymorphism is the most studied gene in AD. This gene has three alleles: ε2, ε3, and ε4. These 3 single nucleotide polymorphisms (SNPs) differ from one another by the presence of either a C or a T nucleotide at codons 112 and 158. These 3 alleles produce 6 different genotypes. Three of the genotypes are homozygous (ε2/ε2, ε3/ε3, and ε4/ε4), and the other 3 are heterozygous (ε2/ε3, ε2/ε4 and ε3/ε4). The distribution of these alleles varies among different ethnicities. Worldwide, the most common allele in all human groups studied up until now is ε3 78% (8.5-98%) followed by ε4 14.5% (0-49%) and ε2 being the least common 6.4% (0-37.5%). The occurrence of APOE-ε4 is strongly linked with late-onset Alzheimer’s disease and may be involved in its pathogenesis. For instance, it has been reported that the mean age of the onset of AD was 68 years in patients with 2 ε4 alleles, 76 years with one ε4 allele, and 84 years in individuals with no ε4 alleles. In contrast, APOE-ε2 appears to protect individuals from AD.

Although the presence of APOE-ε4 increases the probability of the development of AD, it has been shown that the link between ε4 and AD is not necessarily one of cause and effect. In reality, the presence of ε4 is neither sufficient nor essential for the development of AD. This fact emphasizes the importance of gene-environment interaction in the pathogenesis of AD.

In this regard, dyslipidemia is believed to play a role in AD pathogenesis. Actually, APOE alleles have been shown to influence lipid levels. Carriers of ε4 showed higher plasma total and low density lipoprotein (LDL) cholesterol and lower high-density lipoprotein (HDL). Hence, dyslipidemia and genetic susceptibility are among the different potential factors in the etiology of AD.

Therefore, this study aimed to elucidate the frequencies of the APOE alleles and genotypes in AD patients in the Jordanian population. The second aim was to examine the possible relationship between APOE gene polymorphism, lipid profiles, and the risk of developing AD.

**Methods.** Ethics statement. Informed consent was obtained from all participants or legal guardians in accordance with the Institutional Review Board for human study at the University of Jordan, Amman, Jordan.

**Study population samples.** This case-control study included 71 unrelated Jordanian participants: 38 patients with late-onset AD (age ≥65 years) and 33 age-matched healthy controls. All participants were recruited from senior homes and Jordan University Hospital, Amman, Jordan. All blood samples were collected between January 2010 and December 2013. Initially, all participants were screened with the Mini-Mental State Examination (MMSE) and the Clock Drawing Test (CDT). The screening methods were used exactly as they were in a previous study.

The AD patients included in this study were diagnosed as having probable or possible AD according to the criteria of the National Institute of Neurological and Communicative Disorders and the Stroke-Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA). Familial AD patients were excluded from the study using patients’ history.

Individuals in both the AD and control groups had no history of any relevant psychiatric disease or substance abuse and no systemic use of statins, other lipid-lowering agents, and psychotropic drugs.

All control participants failed to meet the diagnostic criteria for AD or dementia but fulfilled the rest of the inclusion criteria. They were screened using 2 scales, the MMSE and the CDT, and scored normally on both rating scales, were functionally independent, and were cognitively healthy Clinical dementia rating=0.

**Lipid profile measurement.** Blood samples were routinely collected in the morning. Recruits were fasting for at least 12 hours (hrs) and less than 16 hrs taking all standard precautions. Serum was separated within...
30 min by centrifugation at 3500 rpm for 10 min and rapidly stored at 4°C until analysis.

The lipid profile measurements included serum total cholesterol (TC), triglycerides (TG), LDL, and high-density lipoprotein (HDL). All samples were measured in the National Center of Diabetes, Endocrinology and Genetics (NCDEG-Jordan) using the Roche Diagnostics COBAS INTEGRA 800 Biochemistry analyzer (USA), which employs an enzymatic colorimetric method.

**DNA extraction.** Venous blood samples (5 ml) were collected in tubes filled with ethylene diamine tetraacetic acid. Genomic DNA was extracted using Puregene Blood Core Kit A (Qiagen, Germany). Isolated DNA was stored at −20°C until use.

**APOE genotyping.** A polymerase chain reaction technique (PCR) was used to amplify APOE gene-exon 4. DNA was amplified using 2 PCR reactions in which 2 primer sets (Integrated DNA Technologies, USA) were used: 1. Set A: AD-F1(5’-ttgggtctctctggctcatc-’3; NC_000019.10: 44908437-44908456) and AD-R1 (5’-ctgcccatctcctccatc-’3; NC_000019.10: 44908821) and AD-R2 (5’-gctggggcttagaggaaatc-’3; NC_000019.10: 44909018-44909001) and 2. Set B: AD-F2 (5’-gccgtagacacctcagaa-’3; NC_000019.10:44908804-44908821) and AD-R2 (5’-gcctggggcttagagaaa-’3; NC_000019.10: 44909432-44909413).

The PCR annealing temperature used for the 2 primer sets was 63°C and 62°C, respectively. The PCR products were analyzed on 1.5% agarose gel containing ethidium bromide. For set A, the PCR product size was 582 bp, while for set B, the product size was 629 bp.

Statistical Analysis Statistical analyses were performed using Statistical Package for Social Sciences (SPSS), Version 18.0. Data were represented as average and standard deviation (age, lipid parameters) or counts and percentage (genotypes and allele types). Deviation from the Hardy Weinberg Equilibrium was assessed using the Chi-square test with one degree of freedom.11 The APOE allele frequencies were estimated by gene counting methods. The Fisher exact test or Chi-square test was used to assess genotype distribution between AD and control subjects. P-values <0.05 were considered statistically significant. Odds ratios (ORs) with 95% confidence intervals (95% CI) were used for categorical variables. Lipid profile variables were compared among different groups using an independent t-test, ANOVA, Man-Whitney test, or Kruskal-Wallis test as appropriate. Selection of parametric tests or non-parametric tests was based on a normality test (Kolmogorov-Smirnov or Shapiro-Wilk) and homogeneity of variance (Leven’s test).

**Results. Study population.** This case-control study included 38 patients with AD and 33 healthy controls. The AD cases collected in this study were 65 to 85 years old.

### Table 1 - Distribution of APOE genotypes frequencies in normal controls and AD patients.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Control n=33</th>
<th>AD n=38</th>
<th>OR</th>
<th>CI</th>
<th>P-value</th>
<th>OR*</th>
<th>CI*</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ε3/ε3</td>
<td>29 (87.9)</td>
<td>23 (60.5)</td>
<td>Ref</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ε2/ε2</td>
<td>1 (3.0)</td>
<td>4 (10.5)</td>
<td>5.0</td>
<td>0.53-48.3</td>
<td>0.18</td>
<td>4.8</td>
<td>0.48-48.6</td>
<td>0.18</td>
</tr>
<tr>
<td>ε2/ε4</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>Ref</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ε4/ε4</td>
<td>0 (0)</td>
<td>1 (2.6)</td>
<td>12.6</td>
<td>1.5-105.8</td>
<td>0.0065</td>
<td>10.6</td>
<td>1.2-92.6</td>
<td>0.033</td>
</tr>
</tbody>
</table>

OR - odds ratio, CI - confidence interval, *values are adjusted to age and gender, †uncalculated due to empty cells, AD - Alzheimer disease, APOE - apolipoprotein E

### Table 2 - Distribution of APOE alleles frequencies in normal controls and Alzheimer’s disease patients.

<table>
<thead>
<tr>
<th>Allele</th>
<th>Control n=33</th>
<th>AD n=38</th>
<th>OR</th>
<th>CI-P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ε3</td>
<td>60 (90.9)</td>
<td>60 (78.9)</td>
<td>Ref</td>
<td>-</td>
</tr>
<tr>
<td>ε2</td>
<td>3 (4.5)</td>
<td>4 (5.3)</td>
<td>1.3</td>
<td>0.29-6.2</td>
</tr>
<tr>
<td>ε4</td>
<td>3 (4.5)</td>
<td>12 (15.8)</td>
<td>4.0</td>
<td>1.07-14.9</td>
</tr>
</tbody>
</table>

OR - odds ratio (not adjusted), CI - Confidence Interval, AD - Alzheimer disease, APOE - apolipoprotein E

### Table 3 - Plasma lipid levels in normal controls and Alzheimer’s disease patients.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Control n=33</th>
<th>AD n=38</th>
<th>P-value</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>187.1±34.6</td>
<td>183.7±41.4</td>
<td>0.7</td>
<td>0.5</td>
</tr>
<tr>
<td>TG</td>
<td>159.6±66.8</td>
<td>161.3±113.7</td>
<td>0.9</td>
<td>0.8</td>
</tr>
<tr>
<td>LDL</td>
<td>113.6±26.4</td>
<td>103.9±32.7</td>
<td>0.2</td>
<td>0.048</td>
</tr>
<tr>
<td>HDL</td>
<td>39.1±12.0</td>
<td>43.8±12.3</td>
<td>0.1</td>
<td>0.06</td>
</tr>
</tbody>
</table>

TC - total cholesterol, TG - triglycerides, LDL - low density lipoprotein, HDL - high-density lipoprotein, AD - Alzheimer disease

APOE polymorphism in Alzheimer patients ... Shafagøj et al

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Neurosciences 2018; Vol. 23 (1) 31
old with a mean age of 74.2±5.4 years and included 24 females (63.2%) and 14 males (36.8%).

Control samples selected in this study were 65 to 88 years old with a mean age of 72.4±6.3 years and included 11 females (33.3%) and 22 males (66.7%). An independent t-test showed no significant difference between the AD group and the control group for age ($p=0.2$), while a Chi-square test showed a significant difference between the groups in gender ($p=0.012$).

APOE genotyping

The genotype distribution of the SNPs was in the Hardy-Weinberg equilibrium for both cases and controls [(SNP112: Alzheimer Disease: $X^2=0.01$, $p=0.99$; Control: $X^2=0.07$, $p=0.8$), (SNP158: Alzheimer Disease: $X^2=0.12$, $p=0.7$; Control: $X^2=0.07$, $p=0.8$)]. The APOE genotype distribution and allele frequencies of the AD patients and the controls are given in Tables 1 and 2. The most common genotype in AD patients was the ε3/ε3 homozygote, followed by the ε3/ε4 heterozygote. The ε3/ε3 genotype was higher in control subjects when compared to AD patients (87.9% vs. 60.5%, $p=0.02$). The ε3/ε4 genotypes were higher in AD patients compared to control subjects (ε3/ε4: 26.3% vs. 3.0%, $p=0.03$). Similarly, the ε4 allele showed a higher incidence in the AD group compared to the control group (15.8% vs. 4.5% respectively; $p=0.03$).

Lipid profile measurement. The mean lipid profile tests, including TC, TG, LDL, and HDL, of AD patients showed no significant difference compared to controls (Table 3).

The relationship between APOE alleles and serum lipid concentrations in AD patients is shown in Table 4. The ε2 allele carriers (ε2+) showed lower total and LDL-cholesterol levels compared to the ε2 non-carriers (ε2-). The opposite effect was noticed with regards to ε4. The total and LDL-cholesterol levels in the ε4 carrier were higher compared to those in ε4 non-carriers. However, none of these differences between the compared groups i.e. ε4 carriers and non-carriers and ε2 carriers and non-carriers were statistically significant ($p>0.05$).

Discussion. Currently, there are no recognized blood biomarkers that facilitate the diagnosis of AD. Therefore, research interest has focused on the identification of asymptomatic individuals with increased risk of AD. Efforts are underway to discover such biomarkers. Dyslipidemia and APOE-ε4 are considered among the potential predictors of AD.

The lipid profile was also examined and linked to APOE genotype. The distribution of the APOE allele in Jordanians was comparable to that of Levant region populations such as Lebanon (ε2 4.3%, ε3 85.9%, and ε4 9.8%) and the Gaza Strip (ε2 5.1%, ε3 87.5%, and ε4 7.3%). We did not find similar studies from other Levant countries such as Syria and Iraq. The Levant region shares geographic location, cuisine, and a probable gene pool, which may explain such similarities in APOE genotype. Comparing our results with non-Levant Arab communities, three different studies from Saudi Arabia showed the total absence of the ε2 allele in healthy Saudis. In addition, data from populations of the Mediterranean basin such as Turks, Greeks, and Sardinians also showed a similar distribution of APOE alleles to that of Jordanians.

The high APOE ε3/ε4 genotype and the ε4 allele frequency among Jordanians with AD is in agreement with other studies that reported similar observations, but still remain lower than that reported in Caucasians, African Americans, and Japanese. Contrary to our findings, others have shown that the possession of the ε4 allele did not increase the risk of AD. Actually, a debate in the literature focused on whether it is the presence of ε4 or the absence of ε2 and ε3 that places individuals at risk for AD.

Table 4 - Lipid profile in AD patients with respect to ε2 and ε4 carriers and non-carriers.

<table>
<thead>
<tr>
<th>Groups</th>
<th>ε2(+) n=4</th>
<th>ε2(-) n=34</th>
<th>P-value</th>
<th>ε4(+) n=11</th>
<th>ε4(-) n=27</th>
<th>P-value</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>170±50</td>
<td>185.3±40.9</td>
<td>0.7</td>
<td>189.7±30.9</td>
<td>181.2±45.3</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>TG</td>
<td>147.2±28.9</td>
<td>162.9±119.9</td>
<td>0.5</td>
<td>125.7±33.0</td>
<td>175.8±131.2</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>LDL</td>
<td>98.3±59.7</td>
<td>104.5±32.4</td>
<td>0.9</td>
<td>111.0±22.3</td>
<td>100.9±36.0</td>
<td>0.6</td>
<td>0.99</td>
</tr>
<tr>
<td>HDL</td>
<td>47.3±16.4</td>
<td>43.4±11.9</td>
<td>0.8</td>
<td>46.5±11.1</td>
<td>42.8±12.8</td>
<td>0.6</td>
<td>0.7</td>
</tr>
</tbody>
</table>

*Values are adjusted to age and gender, only one patient showed ε3(−) which is not enough to achieve sufficient statistical power. Thus, we only reported ε2(+) and ε4(−), the results are expressed as mean±standard deviation, mg/dL, AD - Alzheimer disease, TC - total cholesterol, TG - triglycerides, LDL - low density lipoprotein, HDL - high-density lipoprotein.
the APOE-ε4 allele accounts for the overall genetic risk for AD; however, other genes may also be involved on the pathogenesis of the disease.37

Dyslipidemia is neither specific nor sensitive in predicting the development of AD. Up to date, there is no definite link between high serum cholesterol level and AD; data are not consistent. Nevertheless, few studies have shown that hypercholesterolemia is considered as a risk factor for developing AD, and this risk may be significantly reduced with the use of statins or other lipid-lowering agents.39 In addition, Sabbagh et al30 reported an increase in TC and LDL-C in AD patients, but the cholesterol levels were not linked to the degree of cognitive impairment among those patients. An association between AD pathology and lipid profile has been reported, and this differs in patients with different levels of neurotic plaques in their brain.31 On the other hand, Reitz et al32 concluded that lipid levels and the use of lipid-lowering agents do not seem to be associated with the risk of AD. In addition, Mielke et al33 showed that high cholesterol in late life was even associated with decreased dementia risk. Numerous studies showed a link between the APOE-ε4 allele and dyslipidemia.34-37 Mendez et al38 reported an inverse correlation between plasma triglyceride levels and the number of ε4. Similar to our results, Isbir et al37 also observed high total serum cholesterol in ε4 carriers and low TC in ε2 carriers among AD patients. However, none of these differences were statistically significant (p<0.05). Others have shown that hypercholesterolemic ε4 non-carriers, but not ε4 carriers, are at high risk of developing AD.39 Romas et al40 showed that the link between dyslipidemia and AD was independent of APOE genotype.

Besides the ε4 and lipid profile, AD may be influenced by other factors, such as atherosclerosis, metals such as copper and aluminum, and other unidentified environmental factors.8

Despite its useful findings, this study had a number of limitations. Regarding the distribution of gene polymorphism, this study included a small sample size, especially when only individuals ≥65 years old were selected to participate. The control group was not gender-matched, which could explain the lack of significant data in the subgroup analysis. Thus, future research should use a larger and more representative sample of the general population.

In conclusion, The APOE allele frequency distribution in Jordanians found in this study was similar to the APOE allele frequency distribution in most Arab populations. Our results demonstrated an increased frequency of the APOE-ε4 allele in AD patients versus controls. There was no significant difference in the frequency of the ε2 allele between AD patients and controls. These results support the previous assumption that APOE-ε4 can be considered, at least partly, as a predisposing risk factor for AD susceptibility, and APOE-ε2 may not play a protective role in the development of AD in Jordanians. Lipid profile did not differ between the AD patients and controls. Future studies should involve a larger sample and proper gender matching.

Acknowledgment. We thank the AD patients and their guardians and the control volunteers who agreed to participate in this study. We thank Dr. Eyad Ayoub for his critical review. Also, many thanks to the medical students and Faculty of Medicine at the University of Jordan, Nadeen Faza’, Shauki Quaim, Ihtisam Marashdeh, and Mohammad Abu Arja, for their work in recruiting patients and control subjects and collecting data.

References


Endoscopic transphenoidal approach to skull base lesions

A clinical prospective study

Moneer K. Faraj, MBChB, IFAANS, Wissam J. Sagban, MBChB, FICMS.

ABSTRACT

Objectives: To review the patients operated by endoscopic transphenoidal approach for skull base lesions. All the clinical data including age, gender, type of pathology, surgical outcome and surgical complications were studied.

Methods: A clinical prospective study was conducted on 94 cases with skull base lesion that were treated in Neuroscience Hospital in Baghdad, Iraq between October 2011 and December 2016. We followed each patient for an average of 2 years after surgery to determine most common lesion involving the skull base, age and gender distribution, surgical outcome, complications and hospital accommodation. Freeze system of Storz all the cases in the study.

Result: The majority of our patients were between the ages of 20-29 years. Among the 94 patients, 67% had macro adenomas, followed by craniopharyngioma 11%. The mortality rate was 2.1%, Gross total removal was 57.4%. All patients show improvement of the headache after surgery, visual improvement was noticed in 73.4% and hospital accommodation was 2-5 days. Three patients developed cerebrospinal fluid leak, Infection meningitis developed in 3 patients 3.1%, and 2 patients (2.1%) suffered from hormonal disorders and were referred to endocrinologist for therapy. Diabetes insipidus developed as a temporary complication in 4 cases (4.2%).

Conclusion: Trasphenoidal surgery is relatively safe surgery for properly selected patients.

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The earliest transphenoidal surgery was described in 1901 by Schloffer, Von Eiselsberg, and Kocher. This surgery required external rhinotomy incisions. The endonasal and sublabial approaches were introduced in 1910 by Hirsch and Halstead, respectively. One of the most important advantages of transsphenoidal surgery is its favourable visualization of the anatomical structures. As transsphenoidal surgery evolved, technical advances improved the surgical view of the operative field and the orientation. For a century, the transphenoidal approach was primarily used to resect pituitary and other
sellar tumours. However, the endoscopic endonasal transsphenoidal approach has since been proposed as a minimally invasive surgical modality for treating pathologies of the sellar region. Recently, standard endoscopic endonasal procedures have extended to provide access to para-sellar lesions. This technical expansion offers significant potential for resecting skull base lesions. The sphenoidal sinus is the gateway to the skull base. The endoscopic transsphenoidal approach, combined with extended approaches, will provide access to the whole midline skull base, from the Crista Galli to the craniocervical junction. At present, the bi-portal four-handed technique (cusimano & fenton 1996) is the standard method used nowadays for trans nasal endoscopic surgery for skull base lesions. The objective of the study is to review the patients operated by endoscopic transphenoidal approach for skull base lesions. All the clinical data including age, gender, type of pathology, surgical outcome and surgical complications were studied.

Methods. This study was conducted from October 2011 to December 2016 in the Neuroscience Hospital, Baghdad. Approval from the Hospital Ethics Committee was issued for conducting this study. A total of 94 patients (51 females and 43 males) were included, and each patient was followed for an average of 2 years after surgery. The standard approach was used for lesions involving the sella, para sella and suprasellar region. The extended approach was used for lesions in the anterior (frontal) cranial fossa, petrous apex, clivus and foramen magnum. The freeze system of Storz was used in all patients.

General and neurological examination, blood tests, electrocardiogram, echo study, chest X-ray, brain CT-scan and MRI were performed for all patients. Preoperative endocrine profile and visual field assessment were also carried out. All cases underwent operations under general anaesthesia; lumbar puncture injection with a fluorescent dye was used in cases of CSF rhinorrhoea. After the operation, we measured the electrolytes, fluid balance, and hormones; when necessary, we provided replacement therapy. Antibiotics were provided to all patients and anti-epileptics (carbamazepine) were given to some patients. Consent for inclusion in the study was obtained from the patients and their families.

Excel software used for the data analysis. All patients with large tumors that necessitate combined trans nasal and cranial approach simultaneously were excluded from the study.

Results. The median follow-up period was 2 years. The extent of surgical removal was evaluated from postoperative MRI scans obtained 3 months later. There was more females in our study (n=51; 54%) than males (n=43; 46%), because the majority of our cases had pituitary macroadenoma, which is more common in females. Most patients were 20-29 years of age (45 patients).

The most frequent tumour was pituitary macroadenoma (67%), which was followed by craniopharyngioma (11%) (Figure 1). The majority of macroadenoma cases were females complaining of hormonal disorder and infertility, which accounts for the predominant age being between 20-29 years. Re-operation was needed because of tumor recurrence in 5 patients (5.3%); 3 patients had a pituitary macroadenoma, one a meningioma, and one a craniopharyngioma.

Surgical outcome. Gross total tumour removal was achievable in 54 patients (57.4%) (Table 1). Headache symptoms improved in all cases. Visual field improvement was reported in 69 cases (73.4%); most of these cases had pituitary macroadenomas. Intraoperative bleeding from the cavernous sinus occurred in 3 cases, and it was controlled with the use of gentle pressure and surgery.

The CSF leak developed one week postoperatively in 3 patients. All of these patients had macroadenomas; one patient required surgical intervention and the other improved with conservative treatment. Meningitis occurred in three patients; one patient died because he presented in the late stage, while the other 2 had a good response to medication.

Table 1 - Surgical outcome. N=94

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross total removal</td>
<td>54</td>
<td>(57.4)</td>
</tr>
<tr>
<td>Visual improvement</td>
<td>69</td>
<td>(73.4)</td>
</tr>
<tr>
<td>Headache improvement</td>
<td>94</td>
<td>(100)</td>
</tr>
<tr>
<td>Mortality</td>
<td>2</td>
<td>(2.1)</td>
</tr>
<tr>
<td>Days of hospitalization</td>
<td>2-5 day</td>
<td>Average 3 days</td>
</tr>
<tr>
<td>CSF leak</td>
<td>3</td>
<td>(3.19)</td>
</tr>
<tr>
<td>Infection (meningitis)</td>
<td>3</td>
<td>(3.19)</td>
</tr>
<tr>
<td>Hormonal disorders</td>
<td>5</td>
<td>(5.3)</td>
</tr>
<tr>
<td>Diabetic insipidus</td>
<td>4</td>
<td>(4.2)</td>
</tr>
</tbody>
</table>

Table 1 - Surgical outcome. N=94

Disclosure. Authors have no conflict of interests, and the work was not supported or funded by any drug company.
Diabetes insipidus temporarily developed in 4 patients; 3 of them had macroadenomas, and one patient had a craniopharyngioma. Desmopressin was given to those patients. Hormonal replacement therapy was needed in 2 patients. They were referred to an endocrinologist. Mortality occurred in 2 patients. One did not recover from anaesthesia, and the other developed meningitis 2 weeks after surgery. The latter case did not respond to medications.

**Discussion.** In recent decades, endoscopic endonasal trans-spheroidal surgery has become the most popular choice for neurosurgeons and otolaryngologists to treat lesions of the skull base. This is because of minimal invasiveness, a lower incidence of complications, and lower morbidity and mortality rates compared to the traditional approaches.\(^1\)

In our research on 94 patients who underwent surgery, total gross removal of the tumour was noticed in 52% of the cases. In a study performed by Ensenet J\(^1\) on 40 cases, total removal was achieved in 75% of the cases. In another study performed by Shigetoshi Yano et al\(^1\) of 74 cases, total gross removal was achieved in pituitary adenomas and in 68% of meningiomas.\(^1\)

Macro-adenoma was noted in 67% of cases in our study, which is comparable to studies in which 70% of their cases were macroadenomas.\(^1,12\) Visual function improvement was achieved in 82% of patients in this study, and this improvement was nearly the same as in other studies in which 90% of cases showed visual improvement after surgery.\(^1,12,13\) In both studies, the majority of cases that developed better visual results complained of pituitary macroadenomas.

The CSF leaks occurred in three cases (3.1%). In a study performed by Shi Ge Toshi et al,\(^14\) 9.5% developed a CSF leak.\(^14\) In a study performed in a brain tumour centre (John Wayne Cancer Institute USA), 6 out of 102 patients (5.8%) developed a CSF leak.\(^12\) This variation in the percentage from one study to another is related to the tumour type and size. Larger tumors are more likely to have a CSF leak. The pituitary macroadenoma is the most frequent tumour type to have a post-operative CSF leak.\(^14,16\) This finding is similar to the result found in our study in which all cases that had a CSF leak complained of pituitary macroadenomas. The relatively small percentage of patients with a CSF leak in our study is related to the fact that the diaphragmatic sella was not opened unless there was suprasellar extension of the tumor. For these cases, we used 2 double surgical layers with gelfoam to close the defect, and we added an autologous fat graft from the para-umbilical area.

The majority of our patients were between the age of 20-29 years. In a study of 152 patients performed by Timal Chowdhur, Hemanshu et al,\(^1\) the median age was 38 years. In that study, there was a predominance of males in all age groups;\(^1\) in this study, 54% of patients were females, and the majority of them were complaining of infertility due to macroadenoma.

The hospital stay was 2-5 days in our study, which was similar to other studies.\(^17\) Meningitis developed in 3 patients (3.1%), and other studies reported an incidence of meningitis was of between 0.7-1%,\(^18,19\) such as in a study performed by Cappabianca P et al\(^20\) and a study by Dehdashti AR,\(^21\) Ganna et al\(^20\) in which 200 cases underwent endonasal endoscopic surgery. A high complication rate of meningitis has been reported for craniopharyngioma, while 2 cases in our study had a macroadenoma and one a craniopharyngioma.

Hormonal disorder developed in 2 of our patients (2.1%), requiring therapy, and the rate of diabetes insipidus was 4.2%. A study performed on 444 cases by Fatemi et al\(^22\) reported on 75% of cases with pituitary macroadenomas; there was anterior loss in 5% and permanent diabetes insipidus in 2.1%, as well as 2 patients who had total hypophysectomy.

After transsphenoidal adenomectomy, new unplanned hypopituitarism occurs in approximately 5% of patients, while improved hormonal function occurs in 50% of patients. The likelihood of new hormonal loss or recovery appears to depend on several factors. New hypopituitarism most commonly occurs in patients with tumors larger than 20 mm in size, while hormonal recovery is most likely to occur in younger patients without hypertension and in those without an intraoperative cerebrospinal fluid leak.\(^23,25\)

In conclusion, the trans-spheroidal endoscopic approach from skull base tumors has become a well-established method for treating skull base lesions. However, this approach is technically demanding and requires significant practice. The major factors that
predict the success of the trans-spherial endoscopic approach are appropriate patient selection along with good pre- and post-operative specialized care.

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References

How do physical capacity, fatigue and performance differ in children with duchenne muscular dystrophy compared with their healthy peers?

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ABSTRACT

Objectives: To compare the fatigue levels and energy expenditure of children with Duchenne Muscular Dystrophy (DMD) at different functional levels with healthy children.

Methods: The cross-sectional study was carried out in the Unit of Pediatric Neuromuscular Diseases in the Department of Physiotherapy and Rehabilitation, Faculty of Health Science, Hacettepe University between March 2015 and January 2016. Fifty two children diagnosed with DMD in Level I-III according to the Brooke Functional Classification Scale and 17 healthy children were included in the study. The Six Minute Walk Test (6MWT), Northstar Ambulatory Assessment Scale (NSAA), Physiological Cost Index (PCI), and Timed performance tests were used to assess the children.

Results: Comparison in terms of PCI indicated a difference between Levels 2 and 3, and Levels 1 and 3 (p<0.0083). A difference was found in ascending and descending 4 stairs after 6MWT when fatigue after activity was evaluated.

Conclusion: The walking distances, fatigue levels and energy expenditure of DMD patients were higher than the healthy peers. This difference was more prominent with decreasing functional level.

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Duchenne Muscular Dystrophy (DMD), the most common muscular dystrophy in childhood, is an inherited disease characterized by progressive muscle weakness and affects cardiopulmonary functions and ambulation level.1,2 It makes up 85% of dystrophies and has an unfavorable prognosis. The structure of the dystrophin protein which provides the connection between the extracellular matrix and the cytoskeleton in muscle tissue is disrupted due to deletion, duplication or point mutations in the Xp21.2 region of the dystrophin gene with X-linked recessive inheritance and the protein cannot function.2,4 Although the initial clinical symptoms emerge at the age of one, they usually become visible in the period where they start to walk

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Neurosciences 2018; Vol. 23 (1)
Physical capacity and fatigue in DMD ... Alkan et al

and the preschool period. Duck-like walking, walking on toes, pseudohypertrophy in the gastrocnemius and soleus muscles, Gower’s sign (climbing on oneself by supporting the hands from the thighs while straightening up, legs in the abduction position while getting off the ground) and difficulty in ascending the stairs are seen in these children. While the functional level is preserved between the ages of 3-6 years, a decrease is seen between the ages of 6-8. Functional movements become limited between the ages of 9-12 and the children become dependent on the wheelchair.

One of the most important symptoms in children with DMD is excessive fatigue, identified as the failure of a muscle to maintain the strength expected to perform an activity. Although the etiopathogenesis is yet unknown, genetic factors, metabolic products accumulating in the body, muscle metabolism changes, the disease process, sleep status, activity/rest, disease treatment, psychological states, oxygenation, energy change, homeostatic changes, environmental factors, and social factors are among the relevant factors. Fatigue is also one of the most important factors causing a limitation of exercise and activities. The fatigue and physical activity level are closely related to the functional dysfunction in daily life. Thus, fatigue decreases the physical capability of the individuals, increases dependency levels, and lowers the quality of life.

A close relationship between the fatigue and physical activity level and the functional dysfunction level in daily life is recognized in neuromuscular disorders and patients are recommended to increase their physical activity levels.

Only a few studies are available on the fatigue levels in children with DMD in the literature. We did not come across any study comparing the fatigue and energy levels in children with DMD at various stages with that of healthy children. This study was planned to compare the fatigue levels and energy expenditure of children with DMD at different function levels and healthy children.

Methods. Participants. The cross-sectional study was carried out in the Unit of Pediatric Neuromuscular Diseases in the Department of Physiotherapy and Rehabilitation, Faculty of Health Science, Hacettepe University between March 2015 and January 2016. Children with Duchenne Muscular Dystrophy at the first 3 levels according to the Brooke Lower Extremity Functional Rating Scale and healthy children in a similar age group were included. A total of 52 DMD patients; 18 from Level 1, 17 from Level 2 and 17 from Level 3 together with 17 healthy individuals were included in the study as a result of statistical power analysis. Name, surname, demographic data and physical characteristics such as height, body weight and body mass index (BMI) were recorded for all children. All the DMD patients consisted of children who were regularly followed-up at our unit with a home program and family training and were using an ankle foot orthosis during the night. The children were included in the study after obtaining informed consent from the healthy children and informed consent from their families. Permission was also obtained for the study from Hacettepe University Non-Interventional Clinical Studies Ethics Committee in March 2015. The study was performed in accordance to the Helsinki Declaration.

The inclusion criteria of the cases were determined as: Diagnosed with Duchenne Muscular Dystrophy, aged 6 to 11 years, able to cooperate with the instructions of the physiotherapist, no acute disease, no history of any injury or neurologic or orthopedic surgery within the past 6 months.

Exclusion criteria were the withdrawal of consent and not using steroids.

Outcome measures. Functional status. The functional levels of the cases were identified according to the Brooke Lower Extremity Functional Classification. This classification method was prepared based on the method determined by Vignos et al to identify the functional status of the lower and upper extremity during the clinical evaluation of Duchenne Muscular Dystrophy in 1981. The Brooke Lower Extremity Functional Classification scale evaluates the functional level of children with DMD in 10 levels.

Children in the first 3 levels were selected for this study. Level 1: The child can walk and ascend 4 stairs without help. Level 2: The child can walk and ascend 4 stairs by holding the handrail (walks and ascends the stairs in less than 12 seconds by holding the handrail). Level 3: The child can slowly ascend 4 stairs (walks and ascends the stairs in longer than 12 seconds by holding the handrail).

Six-minutes Walking Test (6MWT). The 6MWT is an accepted evaluation method for physical functional capacity and endurance. Its validity and reliability in

Disclosure. Authors have no conflict of interests, and the work was not supported or funded by any drug company.
DMD has been proven and it is used commonly.\(^1\)\(^5\) It is a submaximal walking test that can easily be used in children to measure the distance they can walk in 6 minutes on level ground. It is a simple and easy-to-use evaluation that does not require a high-technology tool and can be performed at the child’s own walking tempo.\(^3\)

**Fatigue evaluation.** We used the duration of ascending and descending 4 stairs in the evaluation of the acute effect of fatigue in our study.\(^1\)\(^6\) The durations of ascending and descending 4 stairs (as fast as possible and as much as possible without holding the handrail against time) without resting before and after the 6MWT test were recorded by stopwatch. We therefore estimated the fatigue of the children in Level 1, Level 2, and Level 3 and the control groups after the activity with an objective method that expresses physiologic fatigue after activity.

**Energy expenditure.** The easy-to-use Physiological Cost Index (PCI) \([ \text{(walking heart rate)} - \text{(resting heart rate)} ] / \text{(walking speed)} \) was used for 6 minutes to calculate the energy expenditure of the children.\(^1\)\(^7\) The children were seated in a chair for 10 minutes before starting the test and the resting heart rate was measured with a fingertip pulse oximeter. When they were ready, the children were asked to stand up and start to walk. As soon as they started to walk, the chronometer was started and the heart rates were measured again every 3 minutes. They were then asked to sit on the chair again at the end of the 6 minutes, and the heart rate was again measured. The walking distance was recorded to calculate the walking speed. After all parameters were obtained, the PCI, i.e. the energy consumed was calculated.

**Timed performance tests.** Duration from lying supine to standing up, duration of walking/running a distance of 10 meters, and duration of ascending and descending 4 stairs were recorded in order to evaluate the functional performances of the patient group and the healthy group against time.\(^1\)\(^8\)

**Northstar ambulatory assessment scale.** The ambulation level of the DMD patients was evaluated with the North Star Ambulation Assessment (NSAA). North Star Ambulation Assessment is graded as the patient ambulating normally and without help, ambulating with compensation, and unable to perform the activity independently. North Star Ambulation Assessment contains 17 items that evaluate the abilities required to continue functional ambulation such as standing on foot, walking 10 meters, jumping, and running. It is scored between 0 and 34 and conducted without the brace or orthoses used by the child in daily life.\(^1\)\(^9\)

**Statistical analysis.** The IBM Statistical Package for the Social Science Version 20 (IBM Corp., Armonk, NY, USA) program was used for the statistical analyses. The compliance of the variables with the normal distribution was evaluated with Skewness, Kurtosis and Histogram Analysis, the Kolmogorov-Smirnov Test and the variation coefficient. The data were not consistent with a normal distribution. Descriptive analyses were presented as mean±standard deviation and minimum and maximum for numerical data and by using frequency tables for non-numerical data. Data with numerical variables were compared with the Kruskal-Wallis test. Post-hoc analyses for pairwise comparisons were conducted by using the Mann-Whitney U test with Bonferroni correction. The total type-1 error level was accepted as 5% and the \(p\)-value as smaller than 0.05 for statistical significance.

**Results.** Demographic information of the groups Level 1, 2, 3 and the healthy group are shown in Table 1. There was no difference between the children at Level 1, 2, 3 and the healthy group in terms of height, weight and body mass index, but a difference was found between Level 1 and 3 in terms of age (\(p<0.0083\)). Descriptive statistics of PCI, 6MWT, ascending 4 stairs before 6MWT, descending 4 stairs before 6MWT, 10 meters walk/run, and standing from supine used in the study are presented in Table 2. The comparison of the evaluation parameters of the Level 1, 2, 3 groups and the healthy group are shown in Table 3.

A difference was found for ascending and descending 4 stairs after 6MWT when fatigue after activity was evaluated, except the duration of descending the stairs in Level 2. When compared in terms of the 6 minutes walking distance, differences were found between all groups, for example, Level 1 and 2, Level 2 and 3, Level 1 and 3, Healthy group and Level 1, Healthy group and Level 2, and Healthy group and Level 3 (\(p<0.0083\)).

Comparison in terms of PCI revealed a difference between Level 2 and 3, and Level 1 and 3 (\(p<0.0083\)), but not between the other groups.

When compared in terms of ascending 4 stairs before and after 6MWT, a difference was found between all groups, for example, between Level 1 and 2, Level 2 and 3, Level 1 and 3, Healthy group and Level 1, Healthy group and Level 2, and Healthy group and Level 3 (\(p<0.0083\)).

Comparison of the descending 4 stairs before and after 6MWT values revealed a difference between Level 2 and 3, Level 1 and 3, Healthy group and Level 1, Healthy group and Level 2, and Healthy group and Level 3 (\(p<0.0083\)), but no difference between Level
worsened. Although children at Level 1 and Level 2 had similar energy expenditure to the healthy group, their walking distances were very different. This shows that the patients and healthy group show different performances with the same energy expenditure. Level 3 consumed the highest energy among the children with DMD with an energy expenditure 3 times higher than the healthy group. We found the functional level in children with DMD and especially at Level 3 according to the Brooke classification to be important in terms of performance as well as energy expenditure. These results should be taken into account when planning the treatment programs, determining the intensity of exercise, and preventing excess energy expenditure and fatigue in children with DMD.

Exercise limitation can develop in these patients due to the potential destructive effects of the exercises related to neuromuscular disorders as mentioned in the literature. Studies have proven that submaximal exercises are useful in DMD patients since maximal exercise causes fatigue and muscle destruction. Belanger et al examined the contraction of foot dorsal and plantar flexors by having muscular dystrophy patients hit a ball and found more muscle fatigue in the dominant extremity, indicating damage due to excessive use of muscles. The patient group was seen to show more fatigue than the control group with 2 minutes of maximal voluntary contraction of the biceps muscle in a study conducted by Schillings et al on various neuromuscular disorder groups and a healthy group. The 6MWT was used and the estimated fatigue calculated according to the differences in distance walked in the first and sixth minutes of the 6MWT. The largest difference was found in patients with Spinal Muscular Atrophy and a small difference was found with DMD. They reported that the relationship between weakness and fatigue varied according to the disease mechanism as an outcome of the study. When the fatigue of 1 and 2. When compared in terms of the 10 meters walking/running duration, differences were found between all groups (p<0.0083). Comparison of the values for standing from the supine position again showed differences between all groups (p<0.0083). The total NSAA score of the children with DMD showed a difference between Level 1 and 2, Level 2 and 3, and Level 1 and 3 (p<0.016).

**Discussion.** This study was planned to compare the physical capacity, fatigue and performances of children with DMD at different functional levels with healthy children. We found that the walking distance, fatigue level and energy expenditure of the children with DMD were lower than in their healthy peers and that this difference became more prominent as the functional level decreased. Children with DMD performed all the timed performance tests in significantly longer durations than the healthy children and Level 3 consumed the highest energy with an energy expenditure 3 times higher than the healthy group. We believe that the data obtained from our evaluations can be easily put to practical use by physiotherapists and can guide the physiotherapy and rehabilitation procedures of these patients.

The energy expenditure can be measured with sophisticated instruments but the PCI method is easy and practical. This method is based on the proportional relationship of the oxygen used by the individual and the heart rate. Its validity in the measurement of oxygen expenditure has been shown in disabled children walking at their own speed. A study has reported a PCI value of 0.40 for a 9-year-old and 0.20 for a 6-year-old healthy child when walking 10 meters. This indicates that the energy consumed increases with development. The difference in energy expenditure between Level 1 and 3 and between Level 2 and 3 in our study indicated that energy expenditure increased as the functional level increased.
the groups after activity was examined, the duration of ascending and descending the stairs after 6MWT was seen to have increased even in the control group. The largest mean duration increase after 6MWT was experienced by Level 3 children and the smallest by the control group. The physiological fatigue of the children with DMD was seen to increase in relation to worsening functional level. The duration of descending the stairs did not change after 6MWT in Level 2 children. This may have 2 reasons: The children use gravity to their advantage for this activity and also make good use of the postural compensations that develop secondary to the muscle weakness in DMD.

It has been reported that using a combination of the standard evaluation methods such as the NSAA ambulation test, 6MWT, and timed performance tests to determine functionality in DMD patients will provide more effective results compared to using only one of these methods.\(^{27}\) The 6MWT, NSAA and timed performance tests were used in a study conducted on 112 ambulatory children with DMD. The mean 6MWT distance was less than 300 meters in children with a total NSAA score under 17 and 400 meters in those with a total NSAA score over 29.\(^{28}\) A difference was found between the groups in terms of total scores in our study. This result is similar to those reported in other articles. While Level 1 patients had values close to the maximum possible score, their score was also 3 times higher than in Level 3. Martini et al\(^{29}\) evaluated timed performance tests in 14 cases with DMD and investigated the relationship between activity durations and the compensating movements used. These

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean±SD</th>
<th>Upper Limit (%95 CI)</th>
<th>Lower Limit (%95 CI)</th>
<th>Min./Max.</th>
<th>IQR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level 1</strong></td>
<td></td>
<td></td>
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<tr>
<td>PCI (beat/m)</td>
<td>0.25±0.15</td>
<td>0.17</td>
<td>0.33</td>
<td>0.025/0.619</td>
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<td>6MWT (m)</td>
<td>434.02±57.95</td>
<td>405.20</td>
<td>462.84</td>
<td>335/523</td>
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<td>2.59±0.91</td>
<td>2.14</td>
<td>3.05</td>
<td>1.17/4.61</td>
<td>1.38</td>
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<tr>
<td>Descending four stairs before 6MWT (sn)</td>
<td>2.07±0.55</td>
<td>1.79</td>
<td>2.35</td>
<td>1.13/2.91</td>
<td>0.91</td>
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<tr>
<td>Ten meters walk/run (sn)</td>
<td>4.75±0.75</td>
<td>4.38</td>
<td>5.13</td>
<td>3.60/6.12</td>
<td>1.22</td>
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<td>Standing from supine (sn)</td>
<td>4.93±1.74</td>
<td>4.07</td>
<td>5.80</td>
<td>2.33/9.23</td>
<td>2.36</td>
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<td><strong>Level 2</strong></td>
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<tr>
<td>PCI (beat/m)</td>
<td>0.34±0.20</td>
<td>0.24</td>
<td>0.45</td>
<td>0.089/0.752</td>
<td>0.37</td>
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<tr>
<td>6MWT (m)</td>
<td>367.44±63.34</td>
<td>334.35</td>
<td>400.52</td>
<td>255/490</td>
<td>81.50</td>
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<tr>
<td>Ascending four stairs before 6MWT (sn)</td>
<td>4.82±1.66</td>
<td>3.96</td>
<td>5.67</td>
<td>2.34/8.19</td>
<td>5.85</td>
</tr>
<tr>
<td>Descending four stairs before 6MWT (sn)</td>
<td>2.93±1.31</td>
<td>2.25</td>
<td>3.61</td>
<td>1.38/6.81</td>
<td>1.52</td>
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<tr>
<td>Ten meters walk/run (sn)</td>
<td>6.27±1.51</td>
<td>5.49</td>
<td>7.05</td>
<td>4.60/10.30</td>
<td>1.34</td>
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<tr>
<td>Standing from supine (sn)</td>
<td>8.09±2.52</td>
<td>6.80</td>
<td>9.39</td>
<td>3.51/12.06</td>
<td>4.41</td>
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<td><strong>Level 3</strong></td>
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<td>4.31/40.80</td>
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<td>4.31/40.80</td>
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<td>12.98±8.24</td>
<td>8.74</td>
<td>17.22</td>
<td>7.62/43.12</td>
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<tr>
<td>Standing from supine (sn)</td>
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<td>22.53</td>
<td>41.26</td>
<td>12.90/73</td>
<td>28.53</td>
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<td><strong>Healthy Group</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PCI (beat/m)</td>
<td>0.33±0.21</td>
<td>0.21</td>
<td>0.44</td>
<td>0.08/0.91</td>
<td>0.31</td>
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<tr>
<td>6MWT (m)</td>
<td>541.44±62.41</td>
<td>509.34</td>
<td>573.53</td>
<td>415/632</td>
<td>100</td>
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<td>1.57</td>
<td>1.00/2.16</td>
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<td>1.22±0.30</td>
<td>1.06</td>
<td>1.37</td>
<td>0.86/1.90</td>
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<td>2.99</td>
<td>3.47</td>
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<td>1.54</td>
<td>2.03</td>
<td>1.07/2.89</td>
<td>0.65</td>
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</table>

SD - Standard Deviation, PCI - Physiological Cost Index, 6MWT - 6 Minute Walk Test, m - meter, sn - second
compensating movements used in standing from the supine position and ascending and descending from the stairs were found to be related to the activity duration and to be variable.

We found that the children with DMD took significantly longer than healthy children for all the timed performance tests we used in the study. The standing from the supine position duration was 4 times longer in Level 1, 4 times longer in Level 2 and 16 times longer in children with DMD compared to their healthy peers. The ascending and descending the stairs durations were again longer in the children with DMD compared to the healthy children.

As a conclusion, the walking distances, fatigue levels and energy expenditure of DMD patients were higher than the healthy peers. This difference was more prominent with decreasing functional level. The fatigue increases 13 times at Level 3 according to the Brooke classification.

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References

Perioperative lumbar drain utilization in transsphenoidal pituitary resection

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ABSTRACT

Objectives: To evaluate lumbar drain (LD) efficacy in transnasal resection of pituitary macroadenomas in preventing postoperative cerebrospinal fluid (CSF) leak, technique safety, and effect on length of hospital stay.

Methods: We conducted a retrospective data review of pituitary tumor patients in our institution who underwent surgery between December 2006 and January 2013. All patients were operated on for complete surgical resection of pituitary macroadenoma tumors. Patients were divided into 2 groups: group 1 received a preoperative drain, while LD was not preoperatively inserted in group 2. In cases of tumors with suprasellar extension with anticipation of high-flow leak, LD was inserted after the patient was intubated and in a lateral position. Lumbar drain was used for 48 hours, and the drain was removed if no leak was observed postoperatively. In documented postoperative CSF leak patients with no preoperative drain, the leak was treated by LD trial prior to surgical reconstruction. Cases in which leak occurred 6 months postoperatively were excluded.

Results: Our study population consisted of 186 patients, 99 women (53%) and 87 men (47%), with a mean age of 50.3±16.1 years. Complications occurred in 7 patients (13.7%) in group 1 versus 21 (15.5%) in group 2 (p=0.72). Postoperative CSF leak was observed in 1 patient (1.9%) in group 1 and 7 (5%) in group 2 (Fisher exact test=p=0.3). Length of hospital stay was a mean of 4.7±1.9 days in group 1 and a mean of 2.7±2.4 days in group 2 (p=0.001). The most common reason to extend hospital stay was management of diabetes insipidus.

Conclusion: Although LD insertion is generally considered safe with a low risk of complications, it increases the length of hospitalization. Minor complications include headaches and patient discomfort.

Neurosciences 2018; Vol. 23 (1): 46-51

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A pproaches and techniques have advanced since the first description of transsphenoidal surgery (TSS) by Schloffer, Cushing, and Hirsch. The transnasal approach to pituitary and sellar lesions has replaced the sublabial approach as a safer and more effective alternative. Nonetheless, it is not without complications such as cerebrospinal fluid (CSF) leak, diabetes insipidus, and hypopituitarism. Pituitary adenomas are common primary brain tumors in adults representing 25% of cranial neoplasms. The transsphenoidal approach, through the skull base, carries the risk of CSF leak, which is one of the most common complications of skull base operations. It can present either preoperatively, intraoperatively, or postoperatively, and the role of lumbar drain (LD) in each instance is controversial. CSF leak is conservatively managed with LD for 3–5 days or with surgical repair. However, clear guidelines are not present on managing CSF leak following TSS.

Indications for LD use in endoscopic skull base surgery include intracranial hypertension, treatment for postoperative CSF fistula, the use of intrathecal fluorescein, poor or limited reconstructive options (pedicled flaps unavailable), and high-flow CSF leak. Perioperative LD use is speculated to help decrease intracranial pressure and brain swelling by external diversion of CSF, which in turn promotes dural repair healing postoperatively. In addition, it aids in better access to anterior skull base tumors with intraoperative saline infusion. Multiple studies report significant lower rate of postoperative CSF leakage in patients with a preoperatively placed LD. The majority of the study authors use LD rather than prophylactic treatment in case of detection of a CSF leak. This study aim is to evaluate lumbar drain (LD) efficacy in transnasal resection of pituitary macroadenomas in preventing postoperative cerebrospinal fluid (CSF) leak, technique safety, and effect on length of hospital stay.

Methods. We conducted a retrospective data review of adult pituitary tumor patients at our institution who had undergone surgery between December 2006 and January 2013. The sample included cases of pituitary macroadenoma tumors. Patients were divided into 2 groups: group 1 included patients who received a perioperative drain, while group 2 consisted of patients in whom LD was not preoperatively inserted.

In cases of tumors with suprasellar extension, where a high-flow leak is anticipated, LD was inserted in the operating room after the patient was intubated and in a lateral position. It was used for 48 hours, and if no leak was observed after surgery the drain was removed. In patients with documented postoperative CSF leak with no preoperative drain, the leak was treated using a drainage trial prior to surgical reconstruction. Cases of patients in whom the leak occurred 6 months after surgery were excluded. Variables such as complications, presence of postoperative leak, and LD effect on length of hospital stay were investigated, and statistical analysis was performed by the IBM SPSS Statistics for Windows version 23.0 (IBM Corp., Armonk, NY, USA).

Results. Between December 2006 and January 2013, 186 patients who met the inclusion criteria were identified. The population understudy consisted of 99 females (53%) and 87 males (47%) with a mean age of 50.3±16.1 years. Majority of the tumors were nonfunctional in both groups, with 42 (82.3%) nonfunctional tumors in group 1 and 73 (54%) in group 2 (p<0.001). The most prevalent histopathological subtype was non-staining adenoma (Table 1).

Table 2 shows the histopathological characteristics of our population. Cavernous sinus (CS) involvement was noted in 16 patients (31%) in group 1, while 26 patients (19%) in group 2 had CS involvement. Complications occurred in 7 patients (13.7%) in group 1 versus 21 (15.5%) in group 2 (p=0.72). General complications (major and minor) included diabetes insipidus, CSF leak, deep venous thrombosis (DVT), cardiac arrhythmia, electrolyte imbalances, intracranial bleeding, and visual loss. Major complications such as cerebral herniation, pneumocephalus, or meningitis were not observed. Postoperative CSF leak was observed in 1 patient (1.9%) in group 1 and 7 (5%) in group 2 (Fisher exact test=0.3). Methods for treating postoperative CSF leak in both groups are described in Table 3.

The mean length of hospital stay was a mean of 4.7±1.9 days in group 1 and a mean of 2.7±2.4 days in group 2 (p<0.001). Table 1 summarizes the comparison between groups 1 and 2. The most common reason for extending hospital stay was the management of diabetes insipidus. Table 4 summarizes the reasons for extended hospital stay in this case series.

Discussion. The literature is indecisive regarding the efficacy of LD use in TSS in preventing postoperative
LD use in pituitary surgery ... Alharbi et al

Table 1 - Group comparison between groups 1 and 2.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group 1</th>
<th>Group 2</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>51</td>
<td>135</td>
<td>NA</td>
</tr>
<tr>
<td>Postoperative CSF Leak</td>
<td>1 (1.9)</td>
<td>7 (5)</td>
<td>0.3*</td>
</tr>
<tr>
<td>Complications</td>
<td>7 (13.7%)</td>
<td>21 (15.5)</td>
<td>0.72</td>
</tr>
<tr>
<td>LHS (mean±SD)</td>
<td>4.7±1.9 years</td>
<td>2.7±2.4 years</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Functional</td>
<td>7 (19)</td>
<td>62 (45.9)</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

*Fisher exact test due to chi square assumption violation, CSF - cerebrospinal fluid, LHS - Length of hospital stay

Table 2 - Histopathology characteristics of our patients.

<table>
<thead>
<tr>
<th>Histopathology</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-staining adenoma</td>
<td>41</td>
<td>(23.5)</td>
</tr>
<tr>
<td>Prolactin-producing adenoma</td>
<td>26</td>
<td>(14.9)</td>
</tr>
<tr>
<td>FSH-producing adenoma</td>
<td>21</td>
<td>(12)</td>
</tr>
<tr>
<td>LH-producing adenoma</td>
<td>1</td>
<td>(5)</td>
</tr>
<tr>
<td>GH-producing adenoma</td>
<td>19</td>
<td>(10.9)</td>
</tr>
<tr>
<td>ACTH-producing adenoma</td>
<td>21</td>
<td>(12)</td>
</tr>
<tr>
<td>GH-, prolactin-producing adenoma</td>
<td>6</td>
<td>(3.4)</td>
</tr>
<tr>
<td>FSH-, LH-producing adenoma</td>
<td>12</td>
<td>(6.8)</td>
</tr>
<tr>
<td>Alpha-hCG-producing adenoma</td>
<td>3</td>
<td>(1.7)</td>
</tr>
<tr>
<td>ACTH-, LH-producing adenoma</td>
<td>1</td>
<td>(0.5)</td>
</tr>
<tr>
<td>FSH-, alpha-hCG-producing adenoma</td>
<td>7</td>
<td>(4)</td>
</tr>
<tr>
<td>Alpha-hCG-, FSH-, LH-producing adenoma</td>
<td>7</td>
<td>(4)</td>
</tr>
<tr>
<td>TSH-, alpha-hCG-, prolactin-producing adenoma</td>
<td>1</td>
<td>(5)</td>
</tr>
<tr>
<td>TSH-, alpha-hCG-, GH-producing adenoma</td>
<td>1</td>
<td>(5)</td>
</tr>
<tr>
<td>FSH-, LH-, Atypical WHO II-producing adenoma</td>
<td>1</td>
<td>(5)</td>
</tr>
<tr>
<td>Not specified adenoma</td>
<td>2</td>
<td>(1.1)</td>
</tr>
<tr>
<td>ACTH-, FSH-, GH-, prolactin-producing adenoma</td>
<td>1</td>
<td>(5)</td>
</tr>
<tr>
<td>TSH-producing adenoma</td>
<td>1</td>
<td>(5)</td>
</tr>
<tr>
<td>Spindle cell oncocytouma</td>
<td>1</td>
<td>(5)</td>
</tr>
<tr>
<td>Corticotroph cell hyperplasia</td>
<td>1</td>
<td>(5)</td>
</tr>
</tbody>
</table>

TSH - Thyroid Stimulating Hormone, LH - Luteinizing Hormone, HCG - Human chorionic gonadotropin, FSH - Follicle Stimulating Hormone, ACTH - Adrenocorticotropic hormone, GH - growth hormone

Table 3 - Management of patients with postoperative cerebrospinal fluid leak.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Conservatively, by lumbar drain</td>
</tr>
<tr>
<td>2</td>
<td>Conservatively, by lumbar drain</td>
</tr>
<tr>
<td>3</td>
<td>Conservatively, by lumbar drain</td>
</tr>
<tr>
<td>4</td>
<td>Surgical repair</td>
</tr>
<tr>
<td>5</td>
<td>Conservatively, by lumbar drain</td>
</tr>
<tr>
<td>6</td>
<td>Surgical repair</td>
</tr>
<tr>
<td>7</td>
<td>Conservatively, by lumbar drain</td>
</tr>
<tr>
<td>8</td>
<td>Conservatively, by lumbar drain</td>
</tr>
</tbody>
</table>

Table 4 - Reasons for extending hospital stay (comparison between 2 groups).

<table>
<thead>
<tr>
<th>Reasons</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF leak</td>
<td>1 (1.9)</td>
<td>7 (5)</td>
</tr>
<tr>
<td>Nasal bleeding</td>
<td>1 (1.9)</td>
<td>1 (0.74)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>None</td>
<td>1 (0.74)</td>
</tr>
<tr>
<td>Hemodynamic instability</td>
<td>None</td>
<td>1 (0.74)</td>
</tr>
<tr>
<td>Electrolyte abnormalities</td>
<td>None</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (3.9)</td>
<td>None</td>
</tr>
<tr>
<td>Deep venous thrombosis</td>
<td>None</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td>Wound infection</td>
<td>1 (1.9)</td>
<td>None</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>None</td>
<td>1 (0.74)</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>None</td>
<td>1 (0.74)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>None</td>
<td>1 (0.74)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>None</td>
<td>1 (0.74)</td>
</tr>
<tr>
<td>Subdural hematoma</td>
<td>None</td>
<td>1 (0.74)</td>
</tr>
<tr>
<td>Visual loss</td>
<td>1 (1.9)</td>
<td>1 (0.74)³</td>
</tr>
<tr>
<td>Hematuria</td>
<td>None</td>
<td>1 (0.74)</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>None</td>
<td>1 (0.74)</td>
</tr>
<tr>
<td>Diabetes insipidus</td>
<td>None</td>
<td>10 (7.4)</td>
</tr>
<tr>
<td>Thyroid storm</td>
<td>None</td>
<td>1 (0.74)</td>
</tr>
</tbody>
</table>

*Wound infection at abdominal fat graft site, †Due to overpacking during surgical repair, this patient required reoperation, ‡An ophthalmic artery aneurysm was detected and surgically treated, §Related to Foley catheter, CSF - Cerebrospinal fluid

CSF leak and other complications. Placing a LD preoperatively and draining 20–60 ml of CSF as the tumor is removed has been proposed to reduce the incidence of intraoperative CSF leak, hence decreasing postoperative leaks.⁶,⁷ Ransom et al⁸ also suggested that intraoperative CSF diversion by LD reduces the tension on the arachnoid making it less likely to rupture, which in turn alleviates the requirement for sellar floor defect. The introduction of nasoseptal flap by Hadad et al⁹ is believed to have decreased the rate of postoperative CSF leak by 50%;¹⁰ whether it is due to the type of flap alone or the combination of LD use and nasoseptal flap has not yet been determined.

Surgical repair technique. The nasoseptal flap was prepared early during the procedure in cases of macroadenomas with suprasellar extension. The surgical cavity was obliterated using fat graft and then Surgicel (ETHICON, New Jersey, USA). Solid floor reconstruction was performed in all cases using Medpor...
implants (Stryker, Kalamazoo, MI, USA). Next, a layer of TISSEEL (BAXTER, Deerfield, Illinois, USA) was used, and the septal flap was applied followed by nasal packing for 3 days. In cases where leak was not expected but observed, the nasoseptal flap was raised after tumor resection was complete, and the remainder of the floor reconstruction process was performed in a similar manner.

Risk factors. Multiple factors may precipitate a postoperative leak: tumor size, histopathology, redo surgery, intraoperative CSF leak, and obesity. Macroadenomas are associated with a large intrasellar dead space following tumor resection, which aggravates the requirement for surgical reconstruction and increases the risk of postoperative leak. In this case series, perioperative LD was inserted in patients with a suprasellar extension as a high-flow leak was expected. Despite the high likelihood of developing a leak in this group, those patients had a lower rate of postoperative CSF leak (1.9%) (Fisher exact test = 0.3). This observation may be associated with LD utilization or the lack of correlation between tumor size per se and CSF leak after endoscopic endonasal approaches.

While observing patients who developed CSF leak in group 2, the majority (6) of cases were female (85%), and all 7 tumors were nonfunctional adenomas. However, in our sample no significance was observed between postoperative leak and tumor size. Histopathologic subtype and other variables in group 2 are listed in Table 5.

Tumor pathology. Histopathological subtype aids in predicting the behavior of pituitary adenomas in terms of invasion of surrounding structures such as CS, optic chiasm, or regrowth after surgery. The most common histopathological subtype was non-staining adenoma (23.5%), followed by prolactin-secreting adenoma (14.9%), Follicle Stimulating Hormone-secreting adenoma (12%), and adrenocorticotropic hormone (ACTH)-secreting adenoma (12%). ACTH-secreting tumors were also associated with higher CSF leak rates; we found ACTH-secreting adenomas in 2 patients who developed a postoperative leak. In accordance with the literature, the majority of tumors were nonfunctional in both groups, with 42 (82.3%) nonfunctional tumors in group 1 and 73 (54%) in group 2 (p = 0.001).

CSF leak grading. Intraoperative CSF leaks have been subcategorized by flow type and grade. Petal et al proposed that the site and size of the defect determine which vascular tissue flap is utilized in low-flow leaks, while in high-flow leaks reconstruction solely depends on the defect site. In contrast, Esposito et al categorized intraoperative CSF leak into 4 grades, where external CSF diversion by LD for 48 hours is reserved for grade 3 CSF leaks combined with surgical repair.

Complications. Lumbar drain complications are a major concern and cause for decreased utilization of LD. Complications such as pneumocephalus, meningitis, overdrainage, neurological deficit, headache, thromboembolic events caused by activity restriction, and catheter disconnection was reported in a study by Ransom et al, to be higher than what surgeons recognize in endoscopic skull base cases and may outweigh the risk of postoperative leak. Complication rates for LD were reported as low as 3%, and the rate in our study population was similar between the 2 groups (7 [13.7%] and 21 [15.5%] in groups 1 and 2, respectively [p = 0.72]). Fortunately, we did not encounter any cases of pneumocephalus or meningitis and did not witness any mechanical complications.

Major and minor complications were encountered in patients sample understudy; a description of cases with these complications follows. Two patients developed nasal bleeding postoperatively that was treated by nasal packing. One patient developed bradycardia that spontaneously resolved and 2 patients suffered from cerebral salt wasting necessitating hospital admission for sodium replacement.

One patient had a headache 8 days postoperatively, and there was no imaging evidence of an intracranial bleed, cerebral edema, or pneumocephalus that could be attributed to LD utilization. Sinusitis was documented in 3 patients for whom 1 extra day of hospital stay was needed for intravenous antibiotics. Two patients had visual loss; in 1 case, an ophthalmic artery aneurysm was detected, and visual loss was attributed to overpacking during surgical repair in the other case in which the

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Table 5 - Histopathologic subtype and other variables in group 2 patient with postoperative CSF leak.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Histopathology</th>
<th>Functional</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>Adenoma, alpha subunit</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>Adenoma, FSH, alpha-hCG</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>Adenoma, ACTH</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>Adenoma, non-staining</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>Adenoma, ACTH, FSH, GH, prolactin</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>Adenoma, FSH</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>Adenoma, non-staining</td>
<td>No</td>
</tr>
</tbody>
</table>

TSH - Thyroid Stimulating Hormone, LH - Luteinizing Hormone, HCG - Human chorionic gonadotropin, FSH - Follicle Stimulating Hormone, ACTH - Adrenocorticotropic hormone, GH - growth hormone
patient required reoperation. A narcotic overdose manifested by nausea, vomiting, and pleural effusion occurred in 1 case in which the patient required hospital admission. The same patient was readmitted because of hyponatremia and required sodium replacement. New-onset atrial fibrillation was documented in 1 case; however, the patient did not require hospital admission. Intracranial bleeding occurred in 1 case in which the patient was re-operated on, and asymptomatic subdural hematoma occurred in another patient and the case was conservatively managed.

One patient’s postoperative course was complicated by an asystolic cardiac arrest, which required epinephrine, atropine, and Cardio Pulmonary Resuscitation, for which spontaneous circulation quickly returned. We believe that her macroglossia produced an upper airway obstruction after extubation, resulting in aspiration and subsequent hypoxia, which contributed to her hypoxic asystolic arrest.

**Length of hospital stay.** A proposed shortcoming of LD utilization is extended length of hospital stay in cases where CSF diversion has failed to prevent a leak. When comparing both groups, LD utilization increased the length of hospital stay; mean length of hospital stay was 4.7±1.9 years in group 1 versus 2.7±2.4 years in group 2 (p<0.001), a statistically significant difference.

Nonetheless, when comparing both groups (Table 4), the most common reasons for increased hospital stay in group 1 were headache, nasal bleeding, and CSF leak management. In group 2, the most common reasons to extend hospital stay were treatment of diabetes insipidus, CSF leak, electrolyte abnormalities, and DVT. However, we believe that the benefit of preventing CSF leak while using LD outweighs the hazard of extended length of hospital stay once a leak occurs.

Perioperative LD use in TSS is still controversial. Pepper et al compared 2 groups of patients, in which 1 group received LD and the other group did not, and postoperative CSF leak rate was similar in both groups. Further, Zhan et al reported a higher complication rate in the LD group as well as an improvement in postoperative leak by conservative management with no drain in the control group and proposed that 2–10 days should be the required period for repair material to set in. We note that the best use for perioperative LD is in a highly specific subgroup of patients in whom high-flow leak is predicted and in which the patients have risk factors such as redo surgery, radiotherapy, large tumor size, or previous sinus procedures. Nevertheless, higher sample numbers are necessary for further research and for answering this question.

**Limitations.** Unfortunately, data regarding intraoperative CSF leak was not graded in this analysis, and data regarding obesity in our patient sample were not collected. This is a limitation of our retrospective review and an area we aspire to address in the future with further research.

In conclusion, LDs are commonly used for perioperative CSF diversion as a prophylactic measure and/or as treatment for CSF rhinorrhea following transsphenoidal pituitary surgery. The complication risk with the use of LDs is low. Although generally considered safe, LD insertion increases the length of hospitalization. Minor complications include headache and patient discomfort. While complications increase health care costs, the presence of LD alone increases resource utilization by adding extra hospital days, laboratory studies, and/or imaging procedures. Thus, LDs should be prudently utilized.

**References**


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Encephalopathy mimicking non-convulsive status Epilepticus

Ramachandiran Nandbagopal, DM, FRCP; Fathiya Al-Murshedi, MD, FRCPC; Mujahid Al-Busaidi, MD, FRCPC; Amna Al-Busaidi, MD.

ABSTRACT

Primary hyperammonemic encephalopathy due to urea cycle disorders (UCD) typically manifests with episodic unresponsiveness and this clinical entity is not often included in the differential diagnosis of presumed non-convulsive status epilepticus (NCSE). However, this diagnostic consideration has therapeutic implications.

In this report, we document the therapeutic importance of elucidating the specific cause of hyperammonemic encephalopathy that closely mimicked NCSE through 2 unique illustrative cases.

Case Report. Patient 1. A 30-year-old woman, who was hitherto diagnosed with schizoaffective disorder and catatonia elsewhere, presented to the Sultan Qaboos University hospital, Muscat, Oman (in the year 2014) with a 5-year-history of episodic unresponsiveness (akinetic mutism) lasting for several hours to a few days with postictal amnesia; there were no apparent triggers (she did not display any particular aversion or fondness for carbohydrate or protein diet) for these episodes that occurred approximately once every 2 months. She was initially admitted under the psychiatry service [of Sultan Qaboos University Hospital (Muscat, Oman)] with such a typical episode, when an EEG was obtained. Patient information and clinical findings are shown in Figure 1.

Diagnostic assessment and therapeutic interventions. During the EEG recording (on day 3 of hospitalization), she was in coma with her eyes closed and there were continuous, generalized, 2.5 Hz sharp and slow wave discharges (Figure 2A) and she was transferred to the Neurology service. A diazepam (10 mg) trial resulted in the disappearance of the ictal sharp waves and she responded partially to painful stimuli by opening her eyes and localizing to pain (Figure 2B). There were no focal neurological deficits. In view of the continuous discharges at >2 Hz and the apparent clinical and EEG response to diazepam, a diagnosis of probable NCSE was made and she was placed on intravenous sodium valproate 1500 mg/day. On the subsequent day, she was again unresponsive and continuous EEG recording showed similar findings as observed in Figure 2A.

Disclosure. The authors declare no conflicting interests, support or funding from any drug company.
However, from this moment onward, there had been no significant electro-clinical improvement with 10 mg of intravenous midazolam followed by the sequential addition of intravenous levetiracetam, phenytoin and oral topiramate in adequate doses (along with the pulse dose of methylprednisolone for presumed autoimmune encephalitis). Despite the intensive care treatment for presumed refractory NCSE, there was no appreciable clinical recovery. Her MRI brain, CSF study and autoimmune encephalitis antibody panel were unremarkable. Based on the finding of mild hyperammonemia (Figure 3) with a normal liver function test, valproate and topiramate were discontinued. While awaiting for the result of plasma amino acid profile, she was started on the standard protocol for hyperammonemic encephalopathy that consisted of 10% dextrose (with correction of extreme hyperglycemia) and intravenous sodium benzoate and sodium phenyl butyrate as ammonia scavengers. In view of the alarmingly rising hyperammonemia (Figures 1 & 3), she was also started on hemodialysis that failed to provide any definite clinical benefits. Her CT brain showed diffuse cerebral edema and repeat EEG showed nearly iso-electrical recording. At this point of time, the previously submitted plasma amino acid profile returned the following results: citrulline: 199.33 µmol/l (reference range: <55 µmol/l), arginine: 112.86 (reference range: <108.00 µmol/l), Fischer ratio=1.4 (controls: ~3.4), threonine:serine=1.8 (controls:~1.1). She was ultimately diagnosed to have adult onset type II citrullinemia (OMIM #603471) that was further
confirmed genetically by the detection of homozygous deletion encompassing exon 5 of SLC25A13 gene on chromosome 7q21.3 by quantitative polymerase chain reaction.

**Follow-up and outcome.** Although dextrose infusion was discontinued, she died of worsening encephalopathy and refractory cerebral edema 15 days after admission possibly in the context of prior carbohydrate induced biochemical deterioration in citrin deficiency (Figure 3). Consent for publication has been obtained from the patient’s relative.

**Patient 2.** A 19-year-old man was evaluated in the Sultan Qaboos University hospital, Muscat, Oman (in the year 2014) for a 10-year-history of progressive intellectual decline, spastic paraparesis and episodic drowsiness (that was triggered by high protein diet). Patient information and clinical findings are shown in Figure 4 for the timeline picture of the clinical course of patient #2.

**Diagnostic assessment.** He was ultimately diagnosed to have arginase deficiency (OMIM #207800) based on the plasma amino acid profile that showed hyperargininemia (arginine: 406.85 µmol/l) and normal level of citrulline (39 µmol/l) during an episode of mild hyperammonemia (ammonia: 73.43 µmol/l; reference range: 11-51 µmol/l). Molecular genetic testing revealed a homozygous substitution c.914G>T in exon 8 of ARG1 gene on chromosome 6q23.2 that resulted in the amino acid substitution p.Gly305Val. During an episode of drowsiness triggered by high protein diet, his plasma ammonia was 105 µmol/l and EEG (Figure 5A) showed identical findings as in case #1.

**Therapeutic intervention, follow-up and outcome.** As the patient was an already diagnosed case of hyperargininemia, he was maintained on the standard hyperammonemic encephalopathy protocol consisting of intravenous dextrose and ammonia scavenger (B), he was conscious and alert and the corresponding EEG normalized to a posterior dominant alpha background rhythm without any ictal discharges. (Low-frequency filter 1 Hz, high-frequency filter 70 Hz).
subsequently he was continued on the oral formulation of ammonia scavengers and advised to avoid triggers such as high protein diet. The patient’s relative provided consent for publication.

Discussion. Our UCD cases (patient 1-previously undiagnosed adult-onset type II citrullinemia and patient 2-known hyperargininemia) presented with episodic hyperammonemic encephalopathy with or without obvious trigger and the electro-clinical syndrome had a close resemblance to NCSE. While the anticonvulsant therapy provided only transient electro-clinical improvement in patient 1 and was not considered in patient 2 (with the already established diagnosis of arginine deficiency), the clinical outcomes were different following the standard treatment protocol for hyperammonemia. In patient 1, in whom the rare diagnosis of adult-onset type II citrullinemia was not initially recognized, the anticonvulsant therapy was suitably modified by discontinuing sodium valproate and topiramate from the polypharmacy for presumed refractory NCSE when mild hyperammonemia was initially uncovered. However, because of her unusual electro-clinical presentation that was hitherto mistaken for catatonia and schizoaffective disorder for nearly 5 years and the latest episode being refractory to treatment with anticonvulsants, we persisted with the work-up for hyperammonemia. The timely availability of the amino acid result (not a routinely ordered biochemical test for NCSE) could have made a therapeutic difference (by the restriction of carbohydrate from the hyperammonemic encephalopathy treatment protocol in patient 1) by improving the diagnostic categorization to a specific UCD such as adult onset citrullinemia and minimizing the diagnostic and therapeutic delay.

In the context of hyperammonemic encephalopathy, pattern recognition of the amino acid abnormalities carries therapeutic implications. Thus, routine administration of dextrose should be avoided in the setting of adult onset citrullinemia, as carbohydrate loading unfavorably influences the biochemical milieu in citrin deficiency and this biochemical deterioration was also vividly illustrated in patient 1 (Figure 3). For the metabolic crisis of UCD mimicking NCSE, the therapeutic focus should be on improving hyperammonemia (as progressively worsening hyperammonemia has deleterious effects on brain function), instead of the overemphasis on anticonvulsant treatment alone.

To the best of our knowledge, this is the first clinical report of adult-onset type II citrullinemia from Oman. Although adult-onset citrullinemia is panethnic, there are regional differences in the reported frequency of adult-onset citrullinemia cases. For instance, a prevalence of 1:100,000-1:230,000 cases has been reported from east Asian countries such as Japan. At present, except for occasional case reports, population-based epidemiological studies addressing the true prevalence of adult-onset citrullinemia from other parts of the world are lacking. It is possible that this condition remains vastly under-diagnosed in many parts of the world. We hope that the present report will provide an educational impetus in raising awareness and improving the early recognition of this potentially treatable condition.

Our cases provide several learning points (take-away lessons): 1) in an otherwise unexplained encephalopathy mimicking NCSE, plasma ammonia and amino acid profile should be included in the initial laboratory panel in view of the diagnostic and therapeutic implications. Often, the genetic confirmation is not quickly available to guide the diagnostic and therapeutic pursuits at the time of metabolic crisis; 2) the standard therapeutic guideline (that excludes cases of adult-onset type II citrullinemia) suggesting dextrose infusion in primary hyperammonemic encephalopathy should be reviewed and individualized; in particular, carbohydrate restriction should be considered in the rare cases of adult-onset type II citrullinemia; 3) apart from the classical phenotype of spastic paraparesis, additional feature of hyperargininemia includes episodic hyperammonmonic encephalopathy.

We emphasize the importance of recognizing hyperammonemic encephalopathy as an imitator of NCSE, as hyperammonemia is an eminently treatable medical emergency and would prove fatal if not adequately or appropriately treated. Timely review of the amino acid profile can guide therapeutic decisions at the time of metabolic crisis.

References


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**Authorship entitlement**

Excerpts from the Uniform Requirements for Manuscripts Submitted to Biomedical Journals updated November 2003.

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The international Committee of Medical Journal Editors has recommended the following criteria for authorship; these criteria are still appropriate for those journals that distinguish authors from other contributors.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) intellectual content; and 3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.

Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.

An author should be prepared to explain the order in which authors are listed.
Sialidosis type I presenting with a novel mutation and advanced neuroimaging features

**ABSTRACT**

Sialidosis (Neuraminidase deficiency, OMIM# 256550) is a rare autosomal recessive disease with approximate prevalence of 1/5,000,000-1/1,500,000 live births, related to neuraminidase gene (NEU1) (OMIM * 608272) pathogenic variants, leading to neuraminidase (EC 3.2.1.18) deficiency.\(^1\) Due to age of onset and severity, Sialidosis divided into 2 types; milder, late-onset, non-dysmorphic form, characterized by macular cherry-red spot, visual defects, myoclonus, ataxia, and seizures - Sialidosis type 1 and severe, early-onset, dysmorphic form - Sialidosis type 2.\(^2\) Myoclonic movements are known to have many possible causes. Special attention should be given to associated symptoms and signs in patients with ataxia and myoclonus. Progressive myoclonus has been associated with lysosomal storage diseases such as sialidosis type 1. In this report, we present brain examination results of the sialidosis type 1 case by using advanced neuroimaging techniques: volumetric magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), and functional MRI and compare it to 3 controls. Also, this study presents a novel pathogenic variant of the NEU1 gene and describes eye findings.

**Case Report.** **Patient information.** The patient, 24-years-old male, was the first child of non-consanguineous healthy parents, presented to our clinic with 6 years history of progressive gait ataxia and jerky movements. Handling timeline of this case is described in Figure 1.

**Disclosure.** The authors declare no conflicting interests, support or funding from any drug company.
Clinical findings. Neurological examination revealed truncal ataxia, dysarthria, and intentional tremor of the upper limbs, negative myoclonus and stimulus sensitive myoclonus in the arms. Funduscopic examination disclosed bilateral macular cherry-red spots (Figure 2). Patient also had generalized seizures.

Diagnostic assessment. The brain MRI showed mild atrophy (Figure 3A). The patient’s genetic analysis, sequencing of the exons and intron/exon splice sites of NEU1 gene by using Sanger method, identified 2 heterozygous pathogenic variants; previously reported and known to be pathogenic NM_000434:c.625delG (p.Glu209SerfsTer94) variant and novel NM_000434:c.928G>A (p.Asp310Asn) variant.3

One patient with sialidosis type 1 and 3 age-matched healthy control males were selected for the study. The eligibility criteria for control subjects were as follows: normal developmental history, normal findings in radiology and normal neurologic examination.

Subjects underwent MRI by using a 20-channel head coil, 1.5 Tesla clinical scanner (Magnetom Aera, Siemens Healthcare, Erlangen, Germany) at Radiology department. T1-weighted magnetization prepared rapid acquisition gradient-echo sequence, axial and coronal T2-weighted sequence, Blood oxygenation level dependent (BOLD) imaging and twice-refocused DTI. Participants had to stay still, eyes-closed, and remain awake during BOLD imaging.

The DTI data (Figure 3B) were analyzed with DTIStudio, ROleditor and DiffeoMap programs. The raw diffusion-weighted images were processed using a 12-mode affine transformation of Automated Image Registration and then Large Deformation Diffeomorphic Metric Mapping.4 After normalization to the JHU-DTI-MNI “Eve” template, each participant’s original brain space was parcellated into 189 anatomical structures. Finally; the volume, fractional anisotropy
(FA) and mean diffusivity (MD) were measured for each cerebral region for all subjects for 189 parcellated brain structures. The preprocessing of BOLD images was performed with Statistical Parametric Mapping (SPM8) software (The Wellcome Department of Cognitive Neurology, London, UK, http://www.fil.ion.ucl.ac.uk/spm/software/spm8). The preprocessing steps included realignment, coregistration to MPRAGE images, normalization to a standard template, and smoothing with an isotropic Gaussian kernel of Full Width at Half Maximum 6 mm. The ROI-based functional connectivity tests were performed with the Functional Connectivity toolbox. In total 89 Brodmann Areas (BA) were examined using ROI to ROI analysis and functional connectivity values were obtained and voxel-wise comparisons restricted to this ROI were evaluated at $p<0.005$ (uncorrected). To compare the differences between sialidosis type 1 patient and controls, independent-samples t-test was performed. Analysis was conducted using IBM statistical package for the social sciences statistics 22 software with

Figure 3 - Neuroimaging results A) The patient's brain MRI figures (white arrows show atrophy) with axial T1, T2, FLAIR and midsagittal T1. B) The patient's brain DTI data.

Figure 4 - Fractional anisotropy (FA) values for the case and the control subjects.

Figure 5 - Mean diffusivity (MD) values for the case and the control subjects (mm$^2$/s).
considering a p-value<0.05 statistically significant. The volume measurements of brain structures such as cerebellum, precentral gyrus (PreCG), postcentral gyrus (PoCG) and subthalamic nucleus were performed. These measurements are shown in Table 1. The volumes of the selected regions were smaller in the patient compared to the controls.

Diffusion measures for sialidosis type 1 and the control group are shown in Figure 4 and Figure 5. The patient had lower FA in the cerebellum but higher FA in the other regions. The patient had higher MD values in the cerebellum whereas lower MD values in the remaining regions (Figure 4, 5).

The functional connectivity between the left anterior prefrontal cortex (BA-10L) and the right dorsal entorhinal cortex (BA-34R) was lower in the patient. The left inferior temporal gyrus (BA-20L) showed higher connectivity with the right perirhinal cortex (BA-35R) in the patient. The connectivity between right frontal eye fields (BA-8R) and right fusiform gyrus (BA-37R) among the one between BA (8R) and dorsolateral prefrontal cortex (BA-46R) were lower in the patient. The left inferior temporal gyrus (BA-20L) and the right perirhinal cortex (BA-35R) was seen higher connectivity in the patient. Also, the connectivity between BA (8R) and the left inferior parietal lobe was higher in the patient. Also, right angular gyrus (BA-39R) showed less connectivity with the left anterior superior temporal gyrus in the patient.

**Therapeutic intervention.** Patient had generalized seizures and was diagnosed with epilepsy which responded to Levetiracetam therapy. Myoclonus and ataxia also decreased after Levetiracetam treatment.

**Follow-up and outcomes.** No new clinical findings were observed during follow-up examinations, patient continued to be seizure-free under Levetiracetam treatment, myoclonus and ataxia were also decreased, patient encouraged to continue treatment. Because of myoclonus and ataxia patient was frequently falling and because of decrease in this complaints the patient’s balance problem resolved.

**Discussion.** We report here the clinical and the genetic findings of a sialidosis type 1 case with a novel pathogenic variant in the NEU1 gene and neuroimaging features. Genetic analysis revealed heterozygous c.625delG and heterozygous c.928G>A variants in our patient, so determination whether position of this variant is cis or trans, evaluation of family segregation needed. Further investigation revealed that father and elder brother are carriers of c.625delG and mother is heterozygous for c.928G>A variant which proves trans positioning compound heterozygosity in our patient. No clinical findings were observed in family members. Lukong et al previously reported homozygous c.625delG (HGMD: CD000945) frameshift variant in infant with complete absence of neuraminidase activity in the cultured fibroblasts. Reported patient was Turkish origin born as our patient, which may suggest that c.625delG variant allele frequency is higher in Turkish population than world population which explains why this variant was neither found in Exome Aggregation Consortium (ExAC) nor 1000G database. Novel c.928G>A variant in silico analysis (MutationTaster, PolyPhen and SIFT) predicted pathogenicity, this variant was not reported in 1000G and was reported as a singleton in ExAC and can be found (rs759646819) to be clinically unknown significant variant in dbSNP database. Considering all above-mentioned descriptions c.928G>A variant was classified as pathogenic according to American College of Medical Genetics (ACMG) and Genomics and the Association for Molecular Pathology, 2015 guidelines.

We revealed volume changes in different brain structures in sialidosis type 1 case. Our case showed lower volume in the right PrCG and bilateral PoCG but higher volume in left PrCG (Table 1). The patient also had significantly smaller cerebellar volume compared to the control group. He also had higher MD values and lower FA values in cerebellum. The patient had abnormal functional connectivity. Moreover, our functional MRI findings might be normal variation because of the small number of controls.

Lu et al recently carried out a study with 11 sialidosis type 1 patients to show cortical damage using DTI and fMRI. The MRI findings of this study suggests that the posterior parts especially occipital lobe also affected. Functional connectivity from the temporal and occipital lobes to the hippocampus and parahippocampus was decreased which evidenced with the increased MD and altered white matter integrity. These sites are the same with the atrophied regions.

The color fundus photography image shows ‘cherry red spot’ appearance due to whitening of the retina in the perifoveal area in this case. Also, optical coherence tomography (OCT) scans passing through the center of the fovea revealed hyperreflectivity in the nerve fiber layer. Kersten et al showed in a case with sialidosis type 1 the same abnormality in the retinal photography and spectral domain OCT. Perimacular and peripapillary retinal nerve fiber layer thickening was observed in OCT.

The sialidosis type 1 is a very rare cause of myoclonus. There are 4 forms of myoclonus which are cortical, subcortical, spinal and peripheral myoclonus types.
The cortical myoclonus is the most common finding in sialidosis type 1 patients. Our results may contribute to the understanding of the cortical myoclonus pathophysiology.

**Patient perspective.** Because of the mild clinical picture in sialidosis type 1 and good response to Levetiracetam, daily life of patient did not affected very much and patient continued to work but had to change department with less physical work after initiation of treatment.

In conclusion, described here advanced neuroimaging features of a case with sialidosis type 1 caused by a novel pathogenic variant in *NEU1* gene which has not been previously reported maybe a valuable information for explanation of the etiopathogenesis of some symptoms seen in this disease.

**References**


**Case Reports**

Case reports will only be considered for unusual topics that add something new to the literature. All Case Reports should include at least one figure. Written informed consent for publication must accompany any photograph in which the subject can be identified. Figures should be submitted with a 300 dpi resolution when submitting electronically. The abstract should be unstructured, and the introductory section should always include the objective and reason why the author is presenting this particular case. References should be up to date, preferably not exceeding 15.

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Brief Communication

Respiratory support attitudes among pediatric intensive care staff for spinal muscular atrophy patients in Saudi Arabia

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ABSTRACT

Objectives: To explore therapeutic attitude of healthcare providers practicing in pediatric critical care in Saudi Arabia toward patients with Spinal Muscular Atrophy (SMA) Type I, and to explore their awareness about the International Consensus statement for SMA care.

Methods: A cross-sectional survey was conducted in April 2015 during 6th Saudi Critical Care Conference, targeting physicians and respiratory therapists practicing in Pediatric Critical Care.

Results: Sixty participants accepted to participate in this survey. Out of those who answered the questionnaire, 44 were included in the analysis. Majority (66%) of participants were unaware of the International Consensus guidelines for SMA. Endotracheal intubation was reported as an acceptable intervention in SMA patients with acute respiratory failure by 43% of participants. Similarly, chronic home ventilation was agreed by 41% of participants.

Conclusion: A nationwide adaptation of the International SMA Consensus guidelines for children with SMA I is recommended, aiming to decrease variability and standardize their management across various healthcare facilities in Saudi Arabia.

Spinal Muscular Atrophy (SMA) is a congenital, autosomal recessive disease characterized by mutations in the survival motor neurons gene on chromosome 5, which leads to degeneration of the anterior horn cells of the spinal cord and the motor cells of the cranial nerve nuclei. The SMA Type I is the most severe form, with an estimated incidence of 1 in 6,000 to 10,000 live births. It is the leading genetic cause of death in infancy, with a reported life expectancy of fewer than 2 years. The onset of symptoms occur within the first few months of life; with increasing muscle weakness, hypotonia and bulbar involvement leading to lung and chest wall development, hypoventilation, impaired cough and inability to clear airway secretions. Without ventilator support, these patients die ultimately from respiratory insufficiency, the primary cause of mortality in these patients.

A large spectrum of options can be offered for these patients regarding the respiratory support, ranging from either no ventilatory support or emphasis on palliative care, or providing more respiratory support, either by non-invasive ventilation or invasive mechanical ventilation, with or without tracheostomy. Multiples healthcare centers in Saudi Arabia offer variable interventions to patients with neuromuscular diseases, and these interventions may prolong the survival into the second decade of life for SMA I patients. For the treating teams, difficult issues may arise concerning the appropriate goals of treatment and the ethics of offering or withholding life support therapies for SMA I patients.

The purpose of this study is to explore the therapeutic attitude of healthcare providers working in the pediatric critical care domain in Saudi Arabia toward patients with SMA Type I. Another aim was to explore their awareness of the recommendations of the International Consensus statement for standard of care in SMA.

Methods: This is a cross-sectional questionnaire-based survey that was conducted in April 2015. The inclusion criteria were physicians and respiratory therapists working in the domain of Pediatric Critical Care in Kingdom of Saudi Arabia. Other healthcare providers working in other critical care setups were excluded. The survey was distributed during the 6th Saudi Critical Care Conference. Attendees to Pediatric track of this scientific gathering were invited to fill the survey. To improve the recruitment process and to reach for all the target population who may have not been in the conference venue, we circulated an email via Saudi pediatric critical care e-mailing group, followed by 2 reminders within 4 weeks.

The questionnaire was drafted by the authors based on a review of the literature regarding SMA Type I ventilatory support and end of life care. Then a
multidisciplinary team focus group meeting was utilized to produce the final version. Experts from our pediatric critical care unit reviewed the questionnaire. It was then piloted in our pediatric intensive care unit healthcare workers, and tested to ensure and determine its clarity, before sending it to the targeted group. The study intended to investigate the participant’s therapeutic attitude toward respiratory support and acceptable interventions for acute and chronic respiratory failure in SMA I patients, to explore their awareness of the recommendations of the Consensus statement for standard of care in SMA.

The questionnaire was divided into 3 parts. The first part included the demographic variables of the respondents including years of experience, specialty, credential, gender, employment sector (whether university, governmental or private hospital setting) and number of beds in their hospital. The second part enquired on their awareness of the guideline of the International consensus statement for standard of care in SMA. The third part explored their therapeutic attitude and their position toward respiratory support and acceptable interventions for acute and chronic respiratory failure, namely: whether they agree, disagree or if they have a neutral position for each of the following statements: If endotracheal intubation is acceptable in acute exacerbations for SMA type I patients, whether chronic home ventilation is acceptable for SMA type I patients, if treating team should offer tracheostomy for SMA type I patients, and whether to consider withholding mechanical ventilation from SMA type I patients.

This study received prior ethical approval by the Institutional Review Board (IRB) of King Saud University (IRB # E15-1476). Statistical analysis for the data was carried out and the categorical variables were expressed as percentages.

**Results.** Out of 82 staff who were approached, 60 (73%) of them accepted to participate in the survey and answered the questionnaire, but 16 of them were excluded because of incomplete answer of the survey questions. The demographic characteristics of the participants are shown in Table 1.

Physicians’ attitude toward respiratory support and acceptable interventions for acute and chronic respiratory failure for SMA Type I are summarized in Table 2. In this sample, 66% of the participants were not aware of the International Consensus guidelines for standards of care for SMA. When answering if endotracheal intubation is an acceptable intervention for SMA Type I patients who are in acute respiratory failure, 43% of the participants agreed, 36% disagreed to proceed with this intervention and the remaining had a neutral position. Participants who agreed for chronic home ventilation (41%) were marginally more than those who disagreed (36%), while the rest (23%) had a neutral position.

Regarding tracheostomy in SMA I chronically ventilated patients, whether to offer this option for the family or not, 48% of participants stated their refusal to offer this option while 38% agreed for it. On the other hand, the participants who refused the decision to withhold the mechanical ventilation for these patients were slightly higher (54%) than those who supported this decision (46%).

**Discussion.** This study characterized the attitude of the health care providers working in the pediatric critical care domain in Kingdom of Saudi Arabia towards SMA type I patients. This study revealed that only 30% of the respondents were aware of the consensus guidelines for management of SMA type I patients. Moreover, significant variation was noticed regarding their therapeutic attitudes in both situations for acute respiratory exacerbation and for chronic respiratory support.

These variations in the management decisions among participants could be explained by the fact that, treatment options and modalities of SMA type I patients are quite challenging due to paucity of internationally recognized practice guidelines for those patients. Another important factor for such variability could be attributed to the variation in knowledge resources and the difference in centers at which participants were trained and consequently they inherited its common

<table>
<thead>
<tr>
<th>Variables</th>
<th>n (%)</th>
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<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>32 (72.7)</td>
</tr>
<tr>
<td>Female</td>
<td>12 (27.3)</td>
</tr>
<tr>
<td><strong>Credential</strong></td>
<td></td>
</tr>
<tr>
<td>Consultant</td>
<td>20 (45.5)</td>
</tr>
<tr>
<td>Other physicians*</td>
<td>15 (34)</td>
</tr>
<tr>
<td>Respiratory therapist</td>
<td>9 (20)</td>
</tr>
<tr>
<td><strong>Hospital setting</strong></td>
<td></td>
</tr>
<tr>
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</tr>
<tr>
<td>Secondary</td>
<td>7 (16)</td>
</tr>
<tr>
<td><strong>Type of hospital</strong></td>
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<td>40 (90)</td>
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<tr>
<td>Private</td>
<td>4 (10)</td>
</tr>
</tbody>
</table>

Includes fellows, specialists & residents
practice in managing such patients. These factors might result in a broad range of therapeutic options regarding treatment of respiratory failure among such patients and consequently, the same child’s treatment plan may vary from simple palliative care to extensive respiratory support from one care giver to another.6,9

The major accounted milestone was in 2005; when the international standards of care committee for SMA patients was established, and the first International Consensus guidelines were published in 2007.8 The aim of this Consensus guidelines was to reduce the variability of care for SMA type I patients and standardize the therapeutic attitude of health care providers caring for such patients.

These findings are similar to Benson et al10 who conducted an international survey regarding the ventilatpry support attitude towards SMA type I patients, and they reported that only 50% of the respondents were aware of the International Guideline Consensus. Moreover, their survey confirmed the existence of regional differences with regard to the physician’s recommendations for chronic invasive ventilation and wide variability existed even within the same region.10

In this study, the greatest practice variability was noticed regarding the decision whether to offer (or not) the tracheostomy option for the family. Some variability was also noticed among the respondents regarding the decision to withhold the mechanical ventilatory support, as more respondents did not agree on this approach. This diversity of therapeutic attitudes may be partially due to the lack of awareness of the the Consensus Statement for Standard of Care in Spinal Muscular Atrophy guidelines, in addition to other potential influencing factors, such as cultural differences, religious concerns, and variable administrative and legal issues. Moreover, absence of a known curative therapy for such patients, at the time of survey, might influence the decision of some participants regarding their attitude for the invasive interventions in the management of those patients.

Consequently, those patients are being offered different therapeutic options and recommendations in different regions of Kingdom of Saudi Arabia, and this could be another challenge for both the families and the physicians regarding the extent of care for their patients.

This study has been conducted in Kingdom of Saudi Arabia, with its potential benefit to emphasize the major need to standardize the management of SMA I patients across the country. Moreover, more education and updates in the International SMA Consensus guidelines should be conducted and distributed to the physicians working in the domain of Pediatric Critical Care as they are frequently involved in the management of SMA I patients where they can be the primary decision maker for them in different situations. Therefore, their opinion and input regarding these patients may significantly influence the clinical practice and the family decision.

Our study has several limitations, such as the low response rate, however, busy intensivists in these acute critical care settings need to share even such limited responses, as this may highlight the situation further for them, especially for SMA patients who present

<table>
<thead>
<tr>
<th>Consensus statement Recommendation</th>
<th>Statement asked in the survey</th>
<th>Consultants</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Disagree</td>
<td>Neutral</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Disagree</td>
<td>Neutral</td>
</tr>
<tr>
<td>“If noninvasive ventilation fails, nonsitters may be intubated and mechanically ventilated as a short-term measure”</td>
<td>“In acute exacerbation, endotracheal intubation is acceptable for SMA type I patients”</td>
<td>9 (45)</td>
<td>7 (35)</td>
</tr>
<tr>
<td>“If noninvasive ventilation was needed during an acute illness, home noninvasive ventilatory support should be considered.”</td>
<td>“Chronic home Ventilation is acceptable for SMA type I patients”</td>
<td>8 (40)</td>
<td>8 (33)</td>
</tr>
<tr>
<td>“In nonsitters with frequent respiratory infections, tracheotomy and ventilation can be considered but may not improve quality of life or decrease hospitalizations”</td>
<td>“Treating team should offer tracheostomy for SMA type I patients”</td>
<td>12 (60)</td>
<td>9 (37)</td>
</tr>
<tr>
<td>“In nonsitters, care without ventilation support is an option if the burden of management outweighs benefit. Noninvasive ventilation may be used palliatively to facilitate hospital discharge and reduce work of breathing.”</td>
<td>“Will you consider withholding Mechanical Ventilation from SMA type I patients?”</td>
<td>8 (40)</td>
<td>12 (60)</td>
</tr>
</tbody>
</table>
with further respiratory compromise, and families may request further opinion from other local practices and other management options. Our study also has potential selection bias; as the targeted participants were from healthcare providers attending the 6th Saudi Critical Care Conference, however, this was minimized by circulating the survey via Saudi pediatric critical care e-mailing group. Another limitation is that the responses might not correlate with the real practice of the respondents in some situations, as we assessed only their opinion. Patient's management is usually individualized on case-by-case assessment, so differences may arise between the opinion and the actual practice.

**Future directions.** This may be addressed by establishing a national registry for SMA cases. Besides that, conducting a similar questionnaire among pediatricians and neurologists in Saudi Arabia, with more specific details on chronic management and further exploration of the social, religious and resources components, will further highlight the chronic care, considering the ongoing clinical trial for new investigational therapies for SMA.11

In conclusion, this study highlights the limited awareness of health care providers managing SMA type I patients in Kingdom of Saudi Arabia for the International SMA Consensus guidelines for children with SMA I. Therefore a nationwide adaptation of these guidelines is recommended, aiming to decrease variability and standardize the management across various healthcare facilities in Saudi Arabia. More education should be considered to conduct and distribute the guideline to the healthcare providers working in the domain of Pediatric Critical Care across the country.

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ORCID ID: 0000-0002-4389-9322

**References**


Brief Communication

The clinical features of patients concurrent with Guillain-Barré syndrome and myasthenia gravis

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ABSTRACT

Objectives: To evaluate all the coincidence cases of Guillain-Barré syndrome (GBS) and myasthenia gravis (MG).

Methods: We performed web-based research of the overlapping incidence of GBS and MG in studies occurring from 1982 to 2016 and restricted to the English language.

Results: Among 15 cases, an elevated CSF protein level without pleocytosis was found in 10 cases (66.7%); reduced nerve conduction was found in 13 cases (86.6%); a positive repetitive nerve stimulation test occurred in 11 cases (73.3%); anti-AChR antibodies were found in 13 cases (86.6%); anti-GQ1b antibodies were found in 6 cases (40%); a positive edrophonium chloride test was present in 10 cases (66.7%); and a co-occurring thymoma or thymectomy occurred in 4 cases (26.6%). The MG co-occurred with acute inflammatory demyelinating polyneuropathy (AIDP) in 8 cases and with Miller Fisher Syndrome in 5 cases. Treatment in the assessed cases included pyridostigmine (10 cases), prednisolone (7 cases), intravenous immunoglobulin (9 cases), plasmapheresis (3 cases), combined intravenous immunoglobulin and plasmapheresis in one case, and immunosuppressive drugs in 2 cases (azathioprine). Functional outcome was mentioned in 13 patients. The prognosis was favorable in 8 of the 15 recorded patients (Hughes 0-1), and 2 cases resulted in death.

Conclusion: Although comorbidity of GBS and MG is extremely rare, early recognition of this combination of inflammation of peripheral nerves and the neuromuscular junction is of great importance for both initial treatment and a better prognosis.

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Disclosure. This study was funded by the National Natural Science Foundation of China (81271309, 81301016, 81541129) and the Beijing Municipal Administration of Hospitals’ Youth Programme (QML20150303).

Myasthenia gravis (MG) is an autoimmune disorder caused by antibodies against acetylcholine receptors (AchR) targeting the neuromuscular junction, resulting in muscle weakness and fluctuating fatiguability.1 It has distinct immunogenic characteristics and can also be considered a paraneoplastic syndrome associated with thymoma or thymic hyperplasia. Current available treatments include symptomatic pharmacological treatment, immunomodulatory drugs, plasma exchange, thymectomy and other supportive therapies. The prognosis is relatively favorable, with less than five percent mortality.

Guillain-Barré syndrome (GBS) is the most common and most severe acute paralytic neuropathy and is mediated by autoantibodies against myelin proteins or axonal components of peripheral nerves. If unrecognized or overlooked, GBS is associated with high rates of mortality due to acute progressive weakness or respiratory failure. The most common symptoms include limb weakness, areflexia and paralysis. There are several recognizable variants of GBS, including acute inflammatory demyelinating polyradiculoneuropathy (AIDP), Miller Fisher Syndrome (MFS), acute motor axonal neuropathy (AMAN), and acute motor-sensory axonal neuropathy (AMSAN). One of the most common subtype of GBS, MFS is an immune-mediated neuropathy that involves the triad symptoms of acute ophthalmoplegia, ataxia and areflexia in the presence of anti-GQ1b antibodies. Several treatments exist, such as plasma exchange and the administration of intravenous immunoglobulin (IVIG).2

As is well-known, MG and GBS are different autoimmune disorders, affecting the neuromuscular junction and peripheral nerve, respectively. However, the exact pathophysiological process of both MG and GBS remains unclear. It is estimated that the frequency of co-occurrence of MG and GBS is less than 1 in 10 billion.3 To the best of our knowledge, the occurrence of MG and GBS overlap syndrome is quite rare.3-14 Furthermore, only 4 studies have reported the comorbidity of MG and MFS previously.15-18 Here, we review all previously described cases and present a new case of our own. We also aim to summarize the clinical features and to elucidate the cause underlying such a rare overlap syndrome.

Methods. Literature was reviewed using PubMed, Embase, the Cochrane Library and Science Direct from January 1982 to December 2016, and the articles were restricted to those published in English. Key search terms included “Guillain-Barré syndrome”, “acute inflammatory demyelinating polyradiculoneuropathy”, “miller fisher syndrome”, “acute motor axonal
neuropathy”, “acute motor-sensory axonal neuropathy” and “myasthenia gravis”. Patients with combined GBS and MG were identified and their clinical data (such as gender, age, nationality, past history, precipitating factors, clinical presentations, laboratory examinations, CSF findings, variants of GBS, anti-AChR antibody presence, anti-GQ1b antibody presence, thymoma, treatment and outcome) were all comprehensively evaluated. Descriptive statistics were utilized to determine the characteristics of these entities, and their respective frequencies were expressed as percentages.

**Results.** Of the 15 patients in the cases assessed, 6 were female and nine were male. All patients were aged 17-90 years. There were seven Chinese patients, 3 Israeli, 2 American, one Japanese, one Caucasian and one French. Of the 15 patients, 10 had precipitating factors such as upper respiratory infection, fever or watery diarrhea. Most cases had similar symptoms, including extraocular muscle weakness, ptosis and areflexia. An elevated CSF protein level without pleocytosis was found in 10 cases (66.7%); reduced nerve conduction was found in 13 cases (86.6%); a positive repetitive nerve stimulation test occurred in 11 cases (73.3%); anti-AChR antibodies were identified in 13 cases (86.6%); anti-GQ1b antibodies were found in 6 cases (40%); an edrophonium chloride test was positive in 10 cases (66.7%); and a co-occurrence with thymoma or previous thymectomy was present in 4 cases (26.6%). According to the variants of GBS, overlap of MG with AIDP occurred in 8 cases, overlap of MG with MFS in 5 cases, and overlap of MG with AMAN and AMSAN each once. The involved treatments included pyridostigmine (10 cases), prednisolone (7 cases), IVIG (9 cases), plasmapheresis or plasma exchange in 3 cases, combined intravenous immunoglobulin (IVIG) and plasmapheresis in one case, and immunosuppressive drugs in 2 cases (azathioprine). Functional outcome

**Table 1 -** The demographic data and characteristics of comorbid AIDP and MG (8 cases).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
<th>Case 6</th>
<th>Case 7</th>
<th>Case 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Israel</td>
<td>Israel</td>
<td>France</td>
<td>USA</td>
<td>Taiwan/ China</td>
<td>China</td>
<td>Taiwan/ China</td>
<td>China</td>
</tr>
<tr>
<td>Gender</td>
<td>F</td>
<td>F</td>
<td>M</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>M</td>
</tr>
<tr>
<td>Age</td>
<td>60</td>
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<td>45</td>
<td>52</td>
<td>36</td>
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<td>73</td>
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<td>Preceding factors</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Clinical characteristics</td>
<td>Limb weakness, areflexia, ptosis, dyspnea, facial palsy</td>
<td>Limb weakness, areflexia, facial palsy, ptosis, dyspnea</td>
<td>Limb weakness, areflexia, facial palsy</td>
<td>Limb weakness, areflexia, ptosis, dysphagia, ophthalmoplegia</td>
<td>Limb weakness, areflexia, ptosis, ophthalmoplegia</td>
<td>Limb weakness, areflexia, ptosis, dysphagia, ophthalmoplegia</td>
<td>Limb weakness, areflexia, dysarthria, respiratory failure</td>
<td>Limb weakness, areflexia, dysarthria, respiratory failure</td>
</tr>
<tr>
<td>Albumino-cytologic dissociation</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Nerve conduction</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>RNS</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>Anti-AChR antibody</td>
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<td>+</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>Anti-GQ1b antibody</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Edrophonium chloride</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Treatment</td>
<td>-</td>
<td>-</td>
<td>Pyridostigmine</td>
<td>IVIG, steroids, pyridostigmine</td>
<td>Plasma exchange, Pyridostigmine, steroids</td>
<td>IVIG, steroids, pyridostigmine, azathioprine</td>
<td>IVIG, steroids, pyridostigmine</td>
<td>pyridostigmine, IVIG, methylprednisolone</td>
</tr>
<tr>
<td>Thymectomy</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Prognosis</td>
<td>6</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MG - Myasthenia gravis, AIDP - Acute inflammatory demyelinating polyradiculoneuropathy, IVIG - Intravenous immunoglobulin, RNS - Repetitive nerve stimulation, Functional outcome was ranked according to the adopted scale by Hughes: 0 healthy; 1 minor symptoms or signs, able to run; 2 able to walk >5 m without assistance, but unable to run; 3 able to walk >5 m with assistance; 4 bed- or chair-bound; 5 requiring assisted ventilation for at least part of the day; and 6 dead. “+” indicates the patient had precipitating factors from infectious disease. “-” indicates the patient did not have precipitating factors from infectious disease. As for the other parameters, “+” indicates positive findings, and “-” indicates negative findings.
Discussion. The GBS and MG are well described heterogeneous autoimmune disorders characterized by the presence of autoantibodies against several different antigens in peripheral nerves and neuromuscular junctions. The incidence of MG is 10-20 cases per million persons per year and that of GBS is 0.4-1.7 cases per million persons per year. Thus, the co-occurrence of both diseases is extremely rare. Although GBS and MG may have some clinically similar symptoms and neurophysiological findings, the differential diagnosis should be made on the basis of ptosis with or without ophthalmoplegia, distribution of limb weakness, and reflexes. The typical clinical characteristics of GBS and MG may be helpful in diagnosis of this type of overlap syndrome.

In our case study, MG was diagnosed according to clinical features, electrophysiological data, a positive neostigmine test, the presence of anti-AChR antibodies and radiological findings of thymoma. The diagnosis of MFS was established on the basis of the acute clinical course, nerve conduction studies indicating demyelinating polyneuropathy, albuminocytologic dissociation in the CSF, the presence of the crucial triad (ophthalmoplegia, areflexia, ataxia), and the

was mentioned in 13 patients and was ranked according to the adopted scale by Hughes. The prognosis was relatively favorable in 8 of the 15 recorded patients (Hughes 0-1). Two cases resulted in death (one had a diagnosis of AIDP and the other had a diagnosis of AMAN).5,9

Figure 1 - High-resolution chest CT revealed a large 8 cm x 3.3 cm thymoma.

Table 2 - The demographic data and characteristics of comorbid MFS and MG (5 cases).

<table>
<thead>
<tr>
<th>characteristics</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
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<td>USA</td>
<td>Hong Kong/China</td>
<td>Japan</td>
<td>China</td>
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<td>Gender</td>
<td>M</td>
<td>M</td>
<td>F</td>
<td>F</td>
<td>M</td>
</tr>
<tr>
<td>Age</td>
<td>40</td>
<td>43</td>
<td>84</td>
<td>69</td>
<td>72</td>
</tr>
<tr>
<td>Preceding factors</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Clinical characteristics</td>
<td>Limb weakness, areflexia, ptosis, ophthalmoplegia</td>
<td>Ataxia, areflexia, ophthalmoplegia, ptosis</td>
<td>Limb weakness, areflexia, ptosis, ophthalmoplegia, ptosis</td>
<td>Acute bilateral ptosis, ophthalmoplegia, ataxic gait, and areflexia</td>
<td>Acute bilateral ptosis, ophthalmoplegia, diplopia</td>
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<tr>
<td>Albumino-cytologic dissociation</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Nerve conduction</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>RNS</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Anti-AChR antibody</td>
<td>+</td>
<td>+</td>
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</tr>
<tr>
<td>Anti-GQ1b antibody</td>
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<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Treatment</td>
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<td>Pyridostigmine, IVIG</td>
<td>IVIG, Steroid</td>
<td>pyridostigmine, IVIG</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Prognosis</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
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</table>

M - Male, F - Female, MG - Myasthenia gravis, MFS - Miller Fisher Syndrome, IVIG - intravenous immunoglobulin, RNS - repetitive nerve stimulation, Functional outcome was ranked according to the adopted scale by Hughes: 0, healthy; 1, minor symptoms or signs, able to run; 2, able to walk >5 m without assistance, but unable to run; 3, able to walk >5 m with assistance; 4, bed- or chair-bound; 5, requiring assisted ventilation for at least part of the day; and 6, dead. “+” indicates the patient had precipitating factors from infectious disease. “-” indicates the patient did not have precipitating factors from infectious disease. As for the other parameters, “+” indicates positive findings, and “-” indicates negative findings.
The demographic data and characteristics of AMSAN (1 case) and AMAN (1 case).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
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<td>Caucasian</td>
</tr>
<tr>
<td>Gender</td>
<td>M</td>
<td>M</td>
</tr>
<tr>
<td>Age</td>
<td>71(AMSAN)</td>
<td>65(AMAN)</td>
</tr>
<tr>
<td>Preceding factors</td>
<td>Limb weakness, areflexia, ptosis, dysarthria, dysphagia, respiratory failure</td>
<td>Limb weakness, areflexia, ptosis, dysarthria, dysphagia, respiratory failure</td>
</tr>
<tr>
<td>Clinical characteristics</td>
<td>Albumino-cytologic dissociation</td>
<td>IVIG, corticosteroids, pyridostigmine, azathioprine</td>
</tr>
<tr>
<td>Treatment</td>
<td>plasmapheresis, IVIG</td>
<td>-</td>
</tr>
<tr>
<td>Thymectomy</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Prognosis</td>
<td>6</td>
<td>2</td>
</tr>
</tbody>
</table>

M- Male, F - Female, yr - Year, MG - Myasthenia gravis, AMAN - acute motor axonal neuropathy, AMSAN - acute motor-sensory axonal neuropathy, IVIG - intravenous immunoglobulin, RNS - repetitive nerve stimulation. Functional outcome was ranked according to the adopted scale by Hughes: 0, healthy; 1, minor symptoms or signs, able to run; 2, able to walk >5 m without assistance, but unable to run; 3, able to walk >5 m with assistance; 4, bed- or chair-bound; 5, requiring assisted ventilation for at least part of the day; and 6, dead. “+” indicates the patient had precipitating factors from infectious disease,”-” indicates the patient did not have precipitating factors from infectious disease. As for the other parameters, “+” indicates positive findings, and “-” indicates negative findings.

Positive anti-GQ1b antibodies. As a result, according to the clinical characterization, electrophysiological results, laboratory data, the improvement of symptoms with anti-acetylcholinesterase and IVIG treatment, and especially, improvement of symptoms upon thymectomy, the diagnosis of both MG and MFS was established.

Fifteen patients, 9 males and 6 females, were observed. Most of the patients presented with precipitating factors. In accessory examinations, the clinical features, from most to least common, were the presence of anti-AChR antibodies (86.6%), a positive nerve conduction test (86.6%), a positive repetitive nerve stimulation test (73.3%), an elevated CSF protein level in the absence of pleocytosis (66.7%), a positive edrophonium chloride test (66.7%), and the presence of anti-GQ1b antibodies (40%). Furthermore, 4 different variants of GBS were observed, 8 cases of AIDP, 5 of MFS, one of AMSAN and one of AMAN. Immunotherapy treatments included IVIG or plasma exchange, and most of the patients had a good prognosis.

Autoimmunity may play a vital role in the pathology underlying both MG and GBS. First, molecular mimicry, which suggests similarity between infectious agents and self-antigens may initiate concurrent MG and GBS, has been suggested as a possible hypothesis.³ It was proposed that some antibodies may show cross-reactions against both myelin proteins on peripheral nerves and acetylcholine receptors in neuromuscular junctions.¹⁹ Some clinical evidences also support the idea of molecular mimicry between gangliosides (such as GQ1b for MFS) and antecedent infectious agents in patients with GBS. Such a theory has been supported by an experimental study showing that antibodies against AChR from the serum of GBS patients cross-reacted in mice.¹⁹ Second, it has been reported that approximately 8-15% of all MG cases are complicated by autoimmune diseases, such as immune thyroid disease and collagen disease.²⁰ The association of MG or GBS with autoimmune diseases, such as autoimmune thyroiditis, has been previously described.⁵,⁸,¹²

Another hypothesis proposed is that thymoma or thymus hyperplasia-associated multi-organ autoimmunity may also play an important role in the process of autoimmunity. Considering the fact that 4 patients suffered from thymoma in the cases we reviewed, thymoma may be considered to be a condition commonly involved in MG. Lastly, some precipitating illnesses are thought to be driving factors in initiation of autoimmune disorders. If an infection occurs, it may not only induce antibody production to initiate GBS but may also enhance the production of anti-AChR antibodies in neuromuscular junctions, leading to MG.²¹

In summary, the coincidence of GBS and MG should be considered when the presenting features do not fully fit one disease or the other. Although some possible hypotheses have been raised, the underlying mechanisms may warrant future investigation.

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GBS & MG … Yuan et al

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ORCID ID: 0000-0001-6532-5410

References


Ethical Consent

All manuscripts reporting the results of experimental investigations involving human subjects should include a statement confirming that informed consent was obtained from each subject or subject's guardian, after receiving approval of the experimental protocol by a local human ethics committee, or institutional review board. When reporting experiments on animals, authors should indicate whether the institutional and national guide for the care and use of laboratory animals was followed.
Type and etiology of pediatric epilepsy in Jordan. A multi-center study

To the Editor

We have read with interest the distinguished study by Al-Qudah et al on the type and etiology of pediatric epilepsy in Jordan.1 Based on the International League Against Epilepsy (ILAE) 2010 classification, the authors found that 90.2% of patients had one seizure type, (53%) of this type were focal seizures followed by generalized seizures (41.5%) and spasms (5.5%). Distinctive constellations were found in 1.7% of patients. Benign epilepsies with centrotemporal spikes were the most common electro-clinical syndromes (27.1%). Epilepsies attributed to structural-metabolic causes were documented in 41.9% of patients, unknown causes (40.4%), and genetic causes in (17.7%) of patients. Most common causes of structural-metabolic group were due to perinatal insults (32%) and most common causes of the genetic group were the presumed genetic electro-clinical syndromes (93.1%).1 I presume that these results ought to be cautiously taken owing to the presence of the following methodological limitation. The employed ILAE in Al-Qudah et al’s study dates back to 2010. It has been criticized with a need to propose a radical change with the elimination of classical concepts, without maintaining the useful elements and modifying only the parts that reflect obsolete concepts in the light of current scientific evidence.2 Unnecessary confusion has been generated by, for example, eliminating the division between focal and generalized epilepsies, but keeping the concept of focal and generalized epileptic seizures or by proposing a classification that mixes different approaches, electro-clinical criteria, etiology, and so on.2 Recently, ILAE 2017 classification is launched. It is operational (practical) and based on the 1981 classification, extended in 2010. It involves the following changes: “partial” becomes “focal”; awareness is used as a classifier of focal seizures; the terms dyscognitive, simple partial, complex partial, psychic, and secondarily generalized are eliminated; new focal seizure types include automatisms, behavior arrest, hyperkinetic, autonomic, cognitive, and emotional; atonic, clonic, epileptic spasms, myoclonic, and tonic seizures can be of either focal or generalized onset; focal to bilateral tonic-clonic seizure replaces secondarily generalized seizure; new generalized seizure types are absence with eyelid myoclonia, myoclonic absence, myoclonic-atonic, myoclonic-tonic-clonic; and finally seizures of unknown onset may have features that can still be classified.3 This new classification does not represent a radical change, but it allows more flexibility and transparency in naming epilepsy types.3 The clinical implication of ILAE 2017 classification in certain populations showed a higher precision of diagnoses, but at the expense of leaving more epilepsies classifiable only at the mode of onset level.4 I presume that if Al-Qudah et al1 employed ILAE 2017 classification in their study, different results might be obtained.

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Reply from the Author

Prof. Al-Mendalawi comments on methodological limitation of ILAE 2010 report used in our published article in Neurosciences journal.1

The Report of the ILAE Commission on Classification and Terminology, 2005–2009 has attracted a lot of debate regarding its value compared to the ones previously reported,5 but it took about 7 years to publish the new Operational classification of seizure types by ILAE 2017.2 Many distinguished studies have been published using the ILAE 2010 report and our study was carried out in the period 2013-2016, where the report of ILAE 2010 used and got published in 2017.6-7 Prof. Al-Mendalawi said: “I presume that if Al-Qudah et al1 employed ILAE 2017 classification in their study, different results might be obtained”. That is true, but looks like saying if ILAE 1981 classification was employed different results might be also, obtained. I presume what will have the last word in the epilepsy classification, etiology, and terminology are the advances in the fields of neuroimaging, neurophysiology, genomic technology molecular biology and the better understanding of epilepsy in the future. Epilepsy has been a challenging dynamic issue for the scientists and will remain so.

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References


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**Illustrations, Figures, Photographs**

All figures or photographs should be submitted in a high resolution (minimum 300 DPI) electronic version saved in jpeg or tiff format. Original hard copies of all figures may be requested when necessary. Photographs will be accepted at the discretion of the Editorial Board. All lettering, arrows, or other artwork must be done by an artist or draftsman. If arrows are used please ensure they appear in a different color to the background color, preferably black with a white border, or white with a black border. If arrows distinguish different items on the figure then different arrow styles should be used ie. long, short, wide, narrow. Written informed consent for publication must accompany any photograph in which the subject can be identified. Written copyright permission, from the publishers, must accompany any illustration that has been previously published.
MATERNAL MORTALITY RATES ARE ON THE RISE, BUT MORE ACCURATE ESTIMATES ARE NEEDED

January 4, 2018 - A new Birth analysis has uncovered dramatic increases in the rates of maternal mortality—the death of a mother during pregnancy, childbirth, or post-partum—in Texas in recent years. There was an 87% increase when comparing 2011-2015 data with 2006-2010 data. Some of the increase is likely due to increased overreporting of maternal deaths due to errors in the data collection system, however.

An accompanying commentary discusses the impact of poor reporting of maternal deaths on national and international efforts to prevent maternal deaths. “Simply put, if accurate maternal mortality data are not available, prevention efforts remain scattered and unfocused. . . and more women die,” the authors wrote.

“Despite measurement issues, it is clear that the United States maternal mortality rate is considerably higher than in most industrialized countries, and that most of these deaths are preventable,” said Dr. Marian MacDorman, lead author of both the study and the commentary. “The problem is in generating the political will to both improve reporting and to improve health care around the time of birth, to save women's lives.”


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PAST FALLS CAN HELP PREDICT AN INDIVIDUAL’S RISK OF BONE FRACTURE INDEPENDENT OF OTHER FACTORS

January 3, 2018 - Results from a new study in Journal of Bone and Mineral Research indicate that an individual’s history of past falls can help predict their risk of bone fractures, independent of bone mineral density and other clinical factors.

The findings were made in the large Osteoporotic Fractures in Men (MrOS) cohort, comprising 4,365 men in United States, 1,823 in Sweden, and 1,669 in Hong Kong, with an average age ranging from 72.4 to 75.4 years, and average follow-up time from 8.7 to 10.8 years. Even after accounting for results from the Fracture Risk Assessment Tool (FRAX) and/or bone mineral density tests, past falls were associated with a 63%-71% increased risk of a new fracture occurring.

“Whilst the predictive value of falls for future fracture is well-established, these new findings—the result of a successful ongoing collaboration across UK, Sweden, Hong Kong, and the US—inform approaches to clinical fracture risk assessment, demonstrating that the fracture risk associated with prior falls is relevant over and above the risk identified by the current global standard approach of FRAX and bone mineral density,” said lead author Prof. Nicholas Harvey, of the MRC Lifecourse Epidemiology Unit, University of Southampton, UK.


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UP TO 650 000 PEOPLE DIE OF RESPIRATORY DISEASES LINKED TO SEASONAL FLU EACH YEAR

14 DECEMBER 2017 | GENEVA - Up to 650 000 deaths annually are associated with respiratory diseases from seasonal influenza, according to new estimates by the United States Centers for Disease Control and Prevention (US-CDC), the World Health Organization and global health partners.

This marks an increase on the previous global estimate of 250 000 – 500 000, which dates from over ten years ago and covered all influenza-related deaths, including cardiovascular disease or diabetes. The new figures of 290 000 – 650 000 deaths are based on more recent data from a larger, more diverse group of countries, including lower middle income countries, and exclude deaths from non-respiratory diseases.

“These figures indicate the high burden of influenza and its substantial social and economic cost to the world,” said Dr Peter Salama, Executive Director of WHO’s Health Emergencies Programme. “They highlight the importance of influenza prevention for seasonal epidemics, as well as preparedness for pandemics.”

The estimates take into account findings from recent influenza respiratory mortality studies, including a study conducted by the United States Centers for Disease Control and Prevention (US-CDC), published in The Lancet on Thursday (14 December).

According to US-CDC, most deaths occur among people aged over 75 years, and in the world’s poorest regions. Sub-Saharan Africa accounts for the world’s greatest flu mortality risk, followed closely by the Eastern Mediterranean and Southeast Asia.

“All countries, rich and poor, large and small, must work together to control influenza outbreaks before the arrival of the next pandemic. This includes building capacity to detect and respond to outbreaks, and strengthening health systems to improve the health of the most vulnerable and those most at risk,” said Dr Salama.

Nearly all deaths among children under five with influenza-related lower respiratory tract infections occur in developing countries, but the effects of seasonal influenza epidemics on the world’s poorest are not fully known.

WHO is working with partners to assess the global influenza burden of disease by providing guidance and expertise to Member States to measure the influenza disease burden and its economic consequences.

Further surveillance and laboratory studies of other diseases such as cardiovascular disease, which can be influenza-related, are expected to yield substantially higher estimates over the next few years.
WHO News Release

WHO encourages countries to prioritize influenza prevention and produce national estimates to inform prevention policies. Annual influenza vaccination is recommended to prevent disease and complications from influenza infection. Vaccination is especially important for people at higher risk of serious influenza complications and death, and for health workers.

Seasonal influenza is an acute viral infection that spreads easily from person to person and circulates worldwide. Most people recover within a week without requiring medical attention. Common respiratory diseases related to seasonal influenza that can cause death include pneumonia and bronchitis.

WHO’s Influenza Burden of Disease Working Group comprises experts from the All India Institute of Medical Science, the National University of Singapore, the South African National Institute of Communicable Diseases, US CDC, Universidad del Valle de Guatemala and the University of Edinburgh.


DEMENTIA: NUMBER OF PEOPLE AFFECTED TO TRIPLE IN NEXT 30 YEARS

7 DECEMBER 2017 | GENEVA - As the global population ages, the number of people living with dementia is expected to triple from 50 million to 152 million by 2050.

“Nearly 10 million people develop dementia each year, 6 million of them in low- and middle-income countries,” says Dr Tedros Adhanom Ghebreyesus, Director-General of WHO. “The suffering that results is enormous. This is an alarm call: we must pay greater attention to this growing challenge and ensure that all people living with dementia, wherever they live, get the care that they need.”

The estimated annual global cost of dementia is US$ 818 billion, equivalent to more than 1% of global gross domestic product. The total cost includes direct medical costs, social care and informal care (loss of income of carers). By 2030, the cost is expected to have more than doubled, to US$ 2 trillion, a cost that could undermine social and economic development and overwhelm health and social services, including long-term care systems.

First global monitoring system launched

The Global Dementia Observatory, a web-based platform launched by WHO today, will track progress on the provision of services for people with dementia and for those who care for them, both within countries and globally. It will monitor the presence of national policy and plans, risk reduction measures and infrastructure for providing care and treatment. Information on surveillance systems and disease burden data is also included.

“This is the first global monitoring system for dementia that includes such a comprehensive range of data,” said Dr Tarun Dua, of WHO’s Department of Mental Health and Substance Abuse. “The system will not only enable us to track progress, but just as importantly, to identify areas where future efforts are most needed.”

Encouraging results in planning for dementia and support for carers

To date, WHO has collected data from 21 countries (1) of all income levels. By the end of 2018, it is expected that 50 countries will be contributing data.

Initial results indicate that a high proportion of countries submitting data are already taking action in areas such as planning, dementia awareness and dementia-friendliness (such as facilitating participation in community activities and tackling the stigmatization of people living with dementia) and provision of support and training for carers, who are very often family members.
Of the countries reporting data so far:

- 81% have carried out a dementia awareness or risk reduction campaign
- 71% have a plan for dementia
- 71% provide support and training for carers
- 66% have a dementia-friendly initiative.

All of these activities are recommended by WHO in the Global action plan on the public health response to dementia 2017-2025. The Plan provides a comprehensive blueprint for action, in areas including: dementia awareness and dementia-friendliness; reducing the risk of dementia; diagnosis, treatment and care; research and innovation; and support for dementia carers. It suggests concrete actions that can be taken by policy-makers, health- and social-care providers, civil society organizations and people with dementia and their careers. The Plan has been developed with attention to the importance of respecting the human rights of people with dementia and engaging them in planning for their care. Targets against which progress can be measured are included.

**Diagnosis and research require significant effort**

Just 14% of countries reporting data could indicate the number of people being diagnosed with dementia. Previous studies suggest that as many as 90% of people with dementia in low- and middle-income countries are unaware of their status.

The data also highlight the need for rapid scale-up of research. There have been some encouraging signs in funding available for investment in research for a cure for dementia in recent years, but much more needs to be done. The number of articles in peer-reviewed journals on dementia in 2016 was close to 7000. This compares with more than 15 000 for diabetes, and more than 99 000 for cancer during the same year. Research is needed not only to find a cure for dementia, but also in the areas of prevention, risk reduction, diagnosis, treatment and care.

The Observatory will provide a knowledge bank where health and social care authorities, medical professionals, researchers and civil society organizations will be able to find country and regional dementia profiles, global reports, policy guidance, guidelines and toolkits on dementia prevention and care.

**Dementia**

Dementia is an umbrella term for several diseases that are mostly progressive, affecting memory, other cognitive abilities and behaviour and interfering significantly with a person’s ability to maintain the activities of daily living. Women are more often affected than men. Alzheimer’s disease is the most common type of dementia and accounts for 60–70% of cases. The other common types are vascular dementia and mixed forms.

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