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AIMS AND SCOPE

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Editorial

Clinical trials from the past to the present

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Randomized controlled trials provide the highest level of evidence for the way we practice medicine, particularly in our choice of treatment. But the results of these trials often have limited applicability to specific patients, as participants in clinical trials are not exactly the same as the patients who show up in our clinics and hospitals. Even beyond the exclusion and inclusion criteria of clinical trials, other factors distinguish patients in our practices from those in trials. Patients in well-conducted trials are monitored closely, and the data are meticulously collected. While we all like to think we follow our patients carefully and appropriately, does this happen in real life? To address this issue Pragmatic randomized trials were devised. Pragmatic randomized controlled trials hope to make sure that money spent on RCTs is well spent by providing information that actually matters to real-world outcomes.

As teachers, we tell students to read the entire published clinical trial report, not just the abstract and conclusions. Over the years, number of journals and clinical studies published have increased exponentially. Naturally we are not in a position to read all these. Usually, the articles that I merely skim lie outside my sub subspecialty areas of interest, as time constraints make this abridged reading a necessity for survival as an academic and a specialist.

Another issue with trial data are they may be outdated. Trials done 10-20 years ago may not be valid today. Conditions of patients, selection and diagnostic criteria can be different. Life styles then and now are not comparable. Older clinical trials in epilepsy lumped all patients together, specific types of epilepsies were not distinguished but treated with the same drug. Now we know that specific syndromes respond differently to different drugs. So the older data may not be valid today. We also have newer agents targeting specific syndromes. Earlier stroke studies too suffered the same methodological issues. Now we know to distinguish embolic stroke from lacunar strokes and lumping all in one study may bias the results. Multiple sclerosis is another condition with newer drugs available for treatment.

Over the last two decades, clinical trials in MS have established a success rate of 27%, defined as passing phase I, II, III and United States Food and Drug Administration (US FDA) approval. As a result of now having 15 approved disease-modifying therapies (DMTs) for relapsing-remitting MS (RRMS), there is a greater challenge to improve the existing options and to achieve prolonged remission. The increased availability of treatment along with revisions in the diagnostic criteria have changed the clinical trial population and restricted the implementation of placebo-controlled trials. At the same time, an increased understanding of the pathophysiology and natural history of the disease have spurred the development of new outcome measurements. Despite numerous successes in advancing therapies for RRMS, similar progress has not been achieved for patients with progressive forms of MS (PMS), and previously failed trials in PMS have delineated the challenges that must be overcome to develop treatments for PMS. The design of MS trials must take its dynamic landscape into consideration and account for the differences between modern and historical trials. In later trials there is a shift from placebo-controlled trials to active comparator studies, and from traditional to new outcome measurements.

The past 25 years have witnessed substantial developments in the treatment of MS. Advancements in therapeutic agents are a direct result of clinical trials that demonstrated their efficacy. Just as the disease course has been redefined with the advent of DMTs, so have characteristics of trials that continue to test new agents. The present-day MS trial population no longer shares the same baseline characteristics as historical groups and is distinguished by earlier diagnosis and milder disease presentation due to increased availability of treatment. This change is present even in placebo groups, thus complicating the comparison of data across trials. At the same time, active comparator designs have replaced placebo-controlled trials for RRMS, as the latter is no longer ethical in an era of proven therapeutic options. The head-to-head comparison of two agents has increased the required trial sample size and duration to be able to detect significant differences.

At the same time, new options for clinical and neuroimaging outcome measurements are beginning to be used in trials to capture different aspects of the disease process. While traditional measures of relapse (e.g. changes in EDSS and focal MRI lesions) continue to remain the standard of assessment of disease activity, new parameters such as brain volume, PROs, MTR, OCT, NFL have contributed new dimensions to outcomes.

Saman B Gunatilake

Editor

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Review

New pathogens causing CNS infections

Udaya K. Ranawaka[1]

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Abstract

Many emerging infections, mainly viruses, are contributing to the reshaping of the global landscape of central nervous system (CNS) infections. Several new organisms causing CNS infection have been discovered over the last decade, and new neurological syndromes have been described for many other known pathogens. Advances in diagnostic techniques such as modern DNA amplification methods have led to the detection of some of the newly identified pathogens. The global attention generated by disease epidemics has helped in the improved understanding of the neurological complications associated with some known pathogens, such as Zika virus, Ebola virus and Enterovirus D68. A better understanding of the evolution of the new pathogens, their host-vector-environment dynamics, and their disease causation is clearly needed for us to be better prepared to meet these emerging threats.

Central nervous system (CNS) infections produce large numbers of death and disability, especially in resource-limited settings such as Sri Lanka[1,2]. Early targeted treatment is crucial in minimising the deaths and disability[1,3,4]. Early targeted treatment, however, depends on establishing a microbiological diagnosis early, and this appears to be easier said than done. Globally, an aetiology is not detected in 85% of cases suspected CNS infection[5]. Lack of diagnostic facilities in resource-limited settings is an important reason for the low diagnostic yields[1,6], but a definitive cause is not found in over 60% of cases even in studies conducted with good microbiological support in settings without resource limitations[5,7,8]. Studies on the epidemiology of CNS infection in Sri Lanka are limited, but the available data show similar low isolation rates ranging from 0.5% to 27.3%[9,10,11,12,13,14,15].

The global landscape of CNS infections, it seems, is changing. Many factors contribute to this, but a key reason is the emergence and re-emergence of many neurotropic pathogens[15,16]. This review will focus on CNS infections caused by several new organisms described in the last decade. Some of them are newly discovered organisms, whereas some are well known pathogens previously not associated with CNS involvement.

New kids on the block: novel pathogens producing CNS disease

Encephalitis from squirrels: Variegated squirrel Bornavirus

Between 2011 and 2013, three men from the same geographical area (Saxony-Anhalt) in Germany developed an unexplained progressive fatal meningo-encephalitis. Clinical features included confusion, ataxia, myoclonus, ocular paresis, psychomotor slowing and coma, and they died 2-4 months after onset of the illness. MRI changes were seen in cortical areas, basal ganglia and brainstem with meningeal enhancement; spinal cord was not affected. They were breeders of variegated squirrels *(Sciurus variegatoides)* and members of the same squirrel-breeding club, and had exchanged their pet squirrels on many occasions. Two of them had reported bites and scratch injuries by the squirrels[17]. On meta-genomic studies, a new bornavirus (named Variegated squirrel Bornavirus-1; VSBV-1) was detected in CNS samples from the three patients, with detection of viral RNA from brain biopsy tissue and anti-Bornavirus IgG antibodies in blood and CSF. Nearly identical generic sequences were detected from one squirrel[17,18].

Borna viruses are single-stranded RNA viruses. Borna disease (1st described in 1885 among cavalry horses in the town of Borna, Germany) is a well known encephalitic illness in horses and sheep, and is caused by the Borna disease viruses (BoDV). VSBV-1 is considered to be a different virus belonging to the same genus and family[17,19]. There is some debate over the causation of human disease by BoDV-1[17,19]. Interestingly, four cases of human encephalitis due to BoDV-1, with 3 of them transmitted by solid organ transplantation from a single donor, were reported in March 2018, again from Germany[19].

Bocavirus and Encephalitis

Human Bocavirus (HBoV) is a single stranded DNA virus of the Parvovirus family, first described in Sweden in 2005. It has been associated with acute respiratory infections (mainly in children) and gastroenteritis, and has been isolated from respiratory samples (genotype HBoV-1) and stools samples (mainly genotypes HBoV-1,2 and 3) worldwide[20]. More recently, the association of HBoV infection with encephalitis has been reported from several countries. The first report was in 2012, when HBoV-1 and 2 were isolated from Bangladeshi children

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with encephalitis[21]. The second report was from Sri Lanka in 2013, where HBoV-1, 2 and 3 were detected in 5 out of 191 CSF samples from adults and children with CNS infection[11,15]. HBoV-associated encephalitis has subsequently been reported in several case series[22,23].

There is ongoing debate on whether HBoV is a true pathogen or an innocent bystander[20,24]. Diagnosis of HBoV infection is mainly based on genome detection by PCR techniques in biological samples. Culture techniques or animal models for virus isolation are still not available; as such, the true pathogenicity of HBoV remains to be defined. However, the presence of high viral loads and the decline in viral concentrations with symptom resolution are considered to be strongly suggestive of a causal role in pathogenesis[20].

CRESS-DNA viruses and CNS

CRESS-DNA viruses are a group of viruses with circular, replication initiator protein (Rep) encoding, single stranded DNA (CRESS-DNA) genomes. They are the smallest viruses known to infect mammals and carry the smallest genomes among autonomously replicating eukaryotic viruses, containing only the Rep and capsid proteins[12]. Several novel CRESS-DNA viruses have been recently reported to be associated with CNS disease.

A study from Vietnam in 2013 reported the detection of a cyclovirus in two patients with CNS infection of unknown etiology, following a search for novel pathogens causing CNS infection using next generation sequencing; the new virus was named Cyclovirus-Vietnam (CyCV-VN). It was subsequently detected in 4% of 642 CSF specimens from patients with suspected CNS infection. It was also isolated in stools from healthy children suggesting the possibility of food-borne or orofaecal transmission, and in stools from pigs and poultry suggesting the existence of animal reservoirs[25]. In 2015, the identification of two novel CRESS-DNA viruses in Sri Lankan patients with unexplained encephalitis was reported. The genomes of a cyclovirus, named Cyclovirus-Sri Lanka (CyCV-SL), and a gemycircularvirus, named Gemycircularvirus-Sri Lanka (GemyCV-SL), were detected by deep sequencing in one and three out of 201 CSF samples, respectively[12]. This was the first report of an association of encephalitis with a gemycircularvirus, and the second with a cyclovirus (following the report from Vietnam). Another report of gemycircularvirus-associated encephalitis was subsequently reported from China[26]. Another novel cyclovirus has been detected from patients with paraplegia in Malawi[27].

Similar to Bocavirus, the causal importance of these CRESS-DNA viruses in CNS infection is yet to be determined. However, it is pertinent to note that circoviruses, belonging to another genus of CRESS-DNA viruses, have been identified in serum and brain tissue of foxes and pigs with unexplained meningo-encephalitis[28,29].

Old dogs with new tricks: newly described CNS involvement with known pathogens

Zika and the CNS

Zika virus (ZIKV) is an arthropod-borne flavivirus transmitted by *Aedes aegypti* mosquitoes. It was first identified in 1947 in a Rhesus monkey in the Zika forest in Uganda, and the first human infection was reported in Nigeria in 1954[18,30,31]. It gained global attention with its recent pandemic re-emergence, with explosive outbreaks in the Pacific region (2013-14) and the Americas (2015)[18,32]. Interestingly, it followed in the wake of a pandemic of Chikungunya infection, a pattern that had been noted in Africa for decades[32]. Neurological involvement with ZIKV was first noted during these outbreaks; until then ZIKV infection was considered a self-limiting mild or subclinical viral illness[32].

A number of neurological syndromes including Guillain-Barre syndrome (GBS), encephalitis, encephalopathy, myelitis, acute disseminated encephalomyelitis, cerebral vasculopathy leading to strokes, CIDP and sensory neuropathy have been reported with ZIKV infection[30,31,32,33,34,35,36,37]. Of these, GBS appears to be the commonest manifestation[37]. The association with GBS was first described following the French Polynesian outbreak; these cases were of the acute motor axonal neuropathy (AMAN) type, but did not have the typical anti-ganglioside antibody profile of AMAN. In contrast, the majority of GBS cases in a Brazilian study were of demyelinating type[37]. ZIKV-related GBS is characterized by a short latency period following infection and rapid progression[30,31]. The association with recent ZIKV infection was demonstrated by anti-ZiV IgM serology in affected patients[30]. ZIKV associated encephalitis presents as a typical viral encephalitis. MRI changes are seen in subcortical areas, and CSF has a meningitic picture with a polymorphonuclear leucocyte-predominant pleocytosis. Presence of ZIKV in CSF has been demonstrated by RT-PCR and positive culture[33]. Unlike with other flaviviruses encephalitis and other forms of neurological involvement seems to be uncommon with ZIKV[18].

The first evidence of neurotropism of ZIKV was seen in the form of cases of microcephaly and other foetal malformations reported during the 2014-16 outbreaks [38,39,40]. An epidemic of microcephaly was noted in Brazil, with a 20-fold increase in numbers in 2014-15[32]. Women who had ZIKV infection during the first two trimesters of pregnancy were 17 times more likely to deliver a baby with microcephaly[31,40]. The association with ZIKV has been demonstrated by the presence of ZIKV genomes by RT-PCR and IgM antibodies in the CSF and serum of newborns[39]. Further, ZIKV-RNA has been detected in amniotic fluid and placentae of pregnant mothers, and foetal brain tissue of dead infants[36]. Microcephaly is

only one part of what is now recognized as 'congenital Zika syndrome'; other manifestations include cerebral atrophy, intracranial calcifications, neural tube defects, optic nerve abnormalities and hearing loss[31]. It is noteworthy that microcephaly is well documented in association with other viral infections such as rubella and CMV during pregnancy, and it has recently been reported with intrauterine infection with West Nile and Chikungunya viruses[38].

Ebola virus disease

Ebola virus is a single stranded RNA virus of the filovirus family. It was first discovered during two simultaneous outbreaks of Ebola virus disease (EVD) in 1976, in South Sudan and in a village near the Ebola river in the Democratic Republic of Congo[41]. EVD is considered to be a zoonosis, and Old World fruit bats of the Pteropodidae family are believed to be the natural hosts for the virus[41,42]. The virus is transmitted to people by handling of dead or sick forest animals (such as monkeys, chimpanzees, gorillas, antelopes or porcupines), or by contact with infected bats. Human-to-human transmission occurs through blood or body fluids, including sexual transmission[41,42]. To date, EVD outbreaks have been confined to the African continent, but the possibility of transcontinental spread due to global air travel remains a major concern[42].

EVD is a viral haemorrhagic fever with 50-80% case fatality[41,42]. Neurological involvement is considered uncommon[42], but has been reported in up to one-third of patients in some series. Some neurological manifestations (seizures, confusion, meningism, tinnitus and hearing loss) were reported during a 1995 Ebola outbreak in the Democratic Republic of the Congo, however, these were not well documented or investigated[43]. Neurological complications first came into prominence during the largest ever outbreak of Ebola virus infection in West Africa (Guinea, Sierra Leone, Liberia) in 2014-16[18]. The main neurological findings included seizures, encephalopathy, encephalitis, meningitis and frontal lobe dysfunction[18, 44, 45, 46]. Cortical atrophy, subcortical white matter lesions and spinal cord lesions have been reported on MRI[44,45]. Detection of Ebola virus genomes in CSF and serum by RT-PCR is the mainstay of diagnosis[45,46,47]. Serological tests are of limited value as they may be negative in fatal cases[42]. Residual cognitive deficits and neurological sequelae have been reported in many patients[18,45]. The virus is thought to be capable of persisting in immunologically privileged sanctuary sites such as the CNS, and producing late relapsing infection and delayed transmission[18,45]. Several cases of late encephalitis and meningitis among survivors have been reported[45,48].

Enteroviruses and the CNS

Beginning 2012, a large number of cases of acute flaccid paralysis of unexplained aetiology were reported from various regions in the United States. The illness was characterised by rapid onset paralysis and cranial neuropathy, and was termed Acute Flaccid Myelitis (AFM). The weakness was asymmetric, proximal more than distal, and with upper extremity more than lower extremity involvement. CSF showed pleocytosis with elevated proteins, and involvement of spinal cord grey matter and brain stem was seen on MRI. Epidemiological studies revealed a strong association with Enterovirus D68 (EV-D68), which is usually a respiratory pathogen, and the virus was identified in respiratory secretions of affected children[49,50,51]. Long term residual neurological deficits have been reported in many of the children[52].

Enterovirus A71 (EV-A 71) is better known to produce CNS involvement. It usually causes hand, foot and mouth disease (HFMD) in children, and has recently caused large outbreaks in Southeast Asia and the Pacific region[53]. It was first isolated in 1969 from a child with encephalitis in California, USA[54], but gained global attention due to the high rate of neurological complications and case fatality during the more recent outbreaks[53,54]. EV-A71 produces an aseptic meningitis, similar to other enteroviuses. However, unlike them, it is capable of invading the brainstem, cerebellum and spinal cord. Brainstem involvement with damage to the vasomotor and respiratory centres in the medulla is believed to be responsible for the severe pulmonary oedema seen in some patients[55]. The spectrum of neurological disorders includes meningitis, encephalitis, paralytic syndrome, myoclonus, tremors, ataxia, Guillain Barre syndrome and transverse myelitis, with or without the presence of HFMD [53,54,55].

CONCLUSION

Many CNS infections remain undiagnosed, and it is likely that many of these are caused by newly emerging infections. Several such emerging infections have been characterised in the last decade, contributing to the changing landscape of CNS infection. Outbreak investigations have helped define the neurological syndromes associated with some known pathogens (such as Zika, Ebola, EV-A71), whereas searching for elusive pathogens with modern diagnostic methods has enabled the discovery of several novel organisms producing CNS infection (e.g., VSBV-1). The pathogenic role of some of the newer pathogens is yet to be confirmed. No specific treatments or vaccines are currently available for many of these infections, and disease surveillance and prevention are the cornerstones of minimising deaths and disability caused by them. The disease patterns are hauntingly similar to some epidemics from yesteryear (e.g, EV-A 71 and polio), and learning from the past lessons would stand us in good stead in facing the new threats.

Key points

- The global landscape of central nervous system infections is rapidly changing.
- Neurological syndromes caused by many emerging organisms, mainly viruses, have been defined in the last decade.
- Epidemic surveillance and investigation have helped in the characterisation of many such neurological syndromes.
- Advances in diagnostic techniques have led to the discovery of many new pathogens causing central nervous system infections.

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Review

Perioperative risks in neuromuscular diseases: An update

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Abstract

Patients with neuromuscular diseases are at a high risk of peri-operative complications. Recent advances in the management of these disorders have increased the survival rates and the need for surgical procedures related or non-related to the primary disorder. Cardiac and respiratory failure are by far the commonest complications in addition to rhabdomyolysis, malignant hyperthermia, myotonic contractures and peri-operative drug induced complications. Meticulous pre-operative assessment, optimization and a high index of suspicion for complications reduce the risks. Regional anesthesia is generally safer. If general anesthesia is required special precautions should be taken. These may vary form disease to disease and thus a multi-disciplinary approach involving the parent surgical team, neurology team, medical team, intensivist and anesthetist is of paramount importance. In this brief update the perioperative assessment and management of the common complications have been discussed along with a brief insight into the anesthetic drugs that may potentiate complications. A very brief description of the common neuromuscular disorders and respective anesthetic considerations has also been mentioned.

Index words: neuromuscular disorders, peri-operative risks, complications, anesthesia

Introduction

Neuromuscular disorders (a heterogenous group of diseases that affect the skeletal muscles), not very uncommon in the current clinical settings, comprise of hereditary and acquired disorders. Recent advances in the management of neuromuscular disorders have resulted in better survival rates and the need for surgical procedures related or non-related to neuromuscular disorders. This poses a concern for the anesthetists, intensivists, the parent medical and surgical team and the neurology team. Understanding the pathophysiology of each condition facilitates peri-operative planning. Precise preoperative diagnosis prior to anesthesia is ideal though not always feasible. Thus, preplanned strategies should be in place should any complication arise.

Hereditary neuromuscular disorders may be pre-junctional (peripheral neuropathies such as hereditary sensory motor neuropathies, Fredrich's ataxia), post-junctional (dystrophias, myotonias, familial periodic paralysis) and metabolic and mitochondrial (metabolic myopathies, mitochondrial myopathies) disorders. Acquired neuromuscular disorders include pre-junctional disorders (motor neuron disease, multiple sclerosis, Guillain-Barre syndrome, peripheral neuropathies), neuromuscular junctional disorders (myasthenia gravis, Eaton-Lambert syndrome) and post-junctional disorders (critical illness polyneuropathy, critical illness myopathy). Patients with neuromuscular diseases have altered vital functions and an increased risk of morbidity and mortality associated with surgical procedures requiring general anesthesia or sedation. Some anesthetic agents trigger life threatening reactions like malignant hyperthermia, rhabdomyolysis or hyperkalemic cardiac arrest secondary to denervation.

Table 1 summarizes the common neuromuscular diseases encountered in routine clinical practice and some important anesthetic considerations.

Pre-operative assessment and management

A detailed neurological diagnosis is essential to confirm the diagnosis and identify the level of progression when feasible and assess risk during surgery and anesthesia[1]. Patients presenting without a definite diagnosis, particularly with isolated elevated creatinine kinase with or without minor signs should be considered as high risk subjects[2]. Ideally there should be a full discussion with the patient and the family regarding the potential risks and complications, preassessment of functional status and associated comorbid conditions, anesthetic strategies and post-operative care plan. High incidence of cardiac and respiratory complications warrant a through pre-operative assessment of these systems. Further the severity of the cardio-respiratory function does not correlate with the progression of the neuromuscular disorder.

Respiratory assessment: Respiratory involvement varies with each disease. Reduced respiratory muscle strength results in restrictive pulmonary impairment with a progressive decrease in forced vital capacity (FVC), ineffective alveolar ventilation leading to nocturnal hypercapnia and later to diurnal hypercapnia. There is

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inadequate clearance of airway secretions, hypoventilation and impaired cough which predispose atelectasis and respiratory failure. Aspiration and micro aspiration are common with bulbar dysfunction. Respiratory status may be further impaired by sleep apnea, nutritional problems, gastro-esophageal reflux or progressive scoliosis. Anesthetic agents decrease respiratory muscle strength, exacerbate hypoventilation, airway secretion retention, aspiration, obstructive and central apneas. These lead to nosocomial infections, prolonged intubation, tracheostomy and eventually death. Thus, all patients should have an extensive preoperative pulmonary assessment and well planned perioperative and postoperative management plan[3,4,5].

Table 1. Common neuromuscular disorders and anesthetic considerations

Neuromuscular disorder	*Anesthetic considerations*
Hereditary Sensory Motor Neuropathy	• Avoid depolarizing neuromuscular blocking agents • Effects of non-depolarizing neuromuscular blocking agents may be prolonged • Anesthesia can be maintained by intravenous or volatile agents • Respiratory compromise may lead to post-operative ventilation • Neurological deficit should be noted before regional anesthesia
Fredrich's ataxia	• Respiratory failure due to diaphragmatic involvement • Depolarizing neuromuscular blocking agents should be avoided • Risk of aspiration due to upper motor neuron involvement • Negatively inotropic drugs should be used carefully due to myocardial involvement
Duchenne's muscular dystrophy / Becker's muscular dystrophy	• Post-operative respiratory insufficiency • Post-operative cardiac dysfunction related to cardiomyopathies or arrythmias • Post-operative ventilatory support and cardiac monitoring • Appropriate pre-operative assessment • Increased blood loss due to smooth muscle and platelet dysfunction • Hypotensive anesthesia recommended to avoid large blood volume loss • Hypovolemia avoided due to relatively fixed cardiac output secondary to non-compliant ventricles • Volume status should be monitored invasively in potential cases for hypovolemia • Volatile anesthesia and depolarizing neuromuscular blocking agents are avoided in female carriers • Depolarizing neuromuscular agents must be avoided • Non-depolarizing muscular agents sparingly used • Avoid inhalation agents due to rhabdomyolysis • Extreme caution with total intravenous anesthesia and a clean anesthetic machine is advisable • If induction using volatile anesthesia is indicated, then inhalation agents should be discontinued as soon as possible with conversion to total intravenous anesthesia and a clean anesthetic machine

(Continued)

Neuromuscular disorder	*Anesthetic considerations*
Myotonic dystrophy	• Avoid factors that may precipitate myotonia eg. Hypothermia, shivering, mechanical and electrical stimulation • Increased sensitivity to sedatives and analgesics • Depolarizing neuromuscular blocking agents not recommended (may induce generalized muscular contractures) • Anticholinesterases may precipitate contractures due to increased sensitivity to acetylcholine • Peri-operative blood glucose monitoring due to impaired glucose metabolism • Bulbar weakness predisposes to aspiration • Cardiac conduction defects may require pacing
Myotonia congenita	• Avoid depolarizing neuromuscular blocking agents (may induce intractable myotonias) • Avoid cold environments, post-operative shivering, excessive physical manipulation • Non-depolarizing neuromuscular blocking agents / peripheral nerve blocks will not relax contractions • Sodium channel blockers may be useful in breaking the contractures
Hyperkalemic periodic paralysis	• Loop diuretics to aid pre-operative potassium depletion • Avoid drugs causing potassium release from the cells – depolarizing neuromuscular blocking agents, potassium containing fluids • Continuous ECG monitoring • Calcium for emergency treatment of hyperkalemic weakness • Minimize fasting • Infuse glucose containing fuids during fasting • Avoid hypothermia • May remain paralyzed for hours after surgery • Use of volatile agents and non-depolarizing neuromuscular blocking agents is thought to be safe
Hypokalemic periodic paralysis	• Potential link with malignant hyperthermia • Volatile agents should be avoided • Depolarizing muscular agents should not be given • Avoid drugs that cause serum potassium shifts including salt and glucose loads • Maintain normothermia • Ensure serum potassium is within normal range • Avoid anxiety (can precipitate weakness) • May need post-operative ventilation should a peri-operative attack occur • Cardiac arrythmias

(Continued)

Neuromuscular disorder	*Anesthetic considerations*
Metabolic myopathies	• Metabolic monitoring during perioperative phase • Adequate hydration with forced diuresis to avoid myoglobinuria • Glucose and amino acid infusion to aid muscle metabolism • Prevent hypothermia • Prevent shivering
Mitochondrial myopathies	• Temporary pacing in the event of total atrio-ventricular block • Control blood glucose • Avoid prolonged fasting • Infuse sodium lactate • Anticipate post-operative respiratory failure • Aspiration due to impaired swallowing • Low dose volatile inhalation anesthetics and ketamine recommended • Local anesthetics and propofol should be avoided or given in reduced concentration due to depressant effect on mitochondria
Motor neuron disease	• Depolarizing neuromuscular blocking agents should be avoided • Non-depolarizing neuromuscular blocking agents may be used in reduced doses due to increased sensitivity • Respiratory complications including risk of post-operative ventilation, weaning difficulties, infection and atelectasis common
Multiple sclerosis	• Local anesthetics may exacerbate symptoms due to increased sensitivity of demyelinated axons to local anesthetic toxicity • Non-depolarizing neuromuscular blocking agents may be used in normal doses • Depolarizing neuromuscular agents should be used with caution or best avoided if the patient is debilitated • Maintain normothermia as symptoms deteriorate with an increase in temperature (demyelinated axons are more sensitive to heat)
Guillain Barre' syndrome	• Intubation and ventilation most likely required • Invasive monitoring due to risk of autonomic instability • Depolarizing neuromuscular blocking agents avoided (should be avoided even after prolonged period of recovery due to the risk of hyperkalemic cardiac arrest • Increased sensitivity to non-depolarizing neuromuscular blocking agents • Avoid post-operative opioids • Can use epidural anesthesia
Diabetic peripheral neuropathy	• Invasive monitoring due to autonomic instability • Anticipate and manage gastroparesis at induction and post-operative period due to autonomic instability • Maintain normothermia due to increased likelihood of hypothermia

(Continued)

Neuromuscular disorder	*Anesthetic considerations*
Myasthenia gravis	• Relative resistance to depolarizing neuromuscular blocking agents (requires only 10% of normal dose) • Avoid cholinesterase inhibitors (prolong the duration of depolarizing neuromuscular blocking agents and also may precipitate a cholinergic crisis) • Avoid drugs that interfere with neuromuscular transmission • Post-operative ventilation may be needed
Eaton-Lambert Syndrome	• Sensitive to depolarizing neuromuscular blocking agents and non-depolarizing neuromuscular blocking agents • Anticholinesterases can be given • Autonomic dysfunction due to relative lack of acetylcholine • May need post-operative ventilation
Critical illness polyneuropathy /myopathy	• Prevention as there is no specific treatment • Avoid prolonged infusions of non-depolarizing neuromuscular blocking agents specially when high dose steroids are used • Avoid depolarizing neuromuscular blocking agents to prevent cardiac arrest

Pulmonary assessment should include an accurate medical history and physical examination, chest X ray, evaluation for sleep disordered breathing, measurement of respiratory functions and cough effectiveness (forced vital capacity, maximum inspiratory pressure, maximum expiratory pressure, peak cough flow, diurnal pulse oximetry). Patient's respiratory status should be optimized before surgery. Patients with indication for non-invasive ventilation and manual or mechanically assisted cough techniques should be trained in the use of assistive devices pre-operatively[6].

Cardiac assessment: Neuromuscular diseases are associated with cardiac dysfunction, cardiomyopathies and / or abnormalities of the conduction system. With the limited ability to increase cardiac output in response to stress and unrecognized or delayed recognition of the clinical manifestations of heart failure[6,7] further confounded by the negative inotropic effects of volatile and intravenous anesthetic agents, positive pressure ventilation, hypoxemia and acute anemia[8] place the patient at high risk for perioperative cardiac side effects. Sensitization of cardiac muscles to catecholamines and the inhibitory effects in voltage-gated potassium channels induce arrhythmias specially when using volatile anesthetics[1]. Pulmonary hypertension secondary to nocturnal hypoxia is a known complication.

All patients require a comprehensive preoperative cardiac assessment and optimization of cardiac therapies. All patients should have an electrocardiogram and echocardiogram, particularly if not done in the previous 12 months[7,9]. All patients with signs and symptoms of arrythmias should have a Holter monitoring[6,9] and a long QT which suggests Andersen syndrome should be excluded in patients with periodic paralysis as it predisposes them to ventricular arrythmias. Patients with a high degree AV block may need cardiac pacemaker before general anesthesia. Those with severe cardiac dysfunction will benefit from invasive arterial pressure monitoring during general anesthesia and in the post-operative period[10]. Preoperative cardiac evaluation is advocated in patients without primary myocardial dysfunction only if pulmonary hypertension is suspected.

In addition to comprehensive cardiac and pulmonary assessment a general assessment and optimization of the patient's medical status should be considered with respect to reducing perioperative complications and enhancing recovery. Poor nutritional balance leads to poor wound healing, inability to clear secretions and maintain adequate ventilation and associated respiratory complications. Thus, a nutritionist assessment and nutritional optimization is mandated[3,11]. Increased sensitivity to premedication drugs could result in sleep apnea and hypoventilation[12]. Patients on chronic treat-

ment with steroids may have suppression of the hypothalamic-pituitary-adrenal axis and susceptible to develop adrenal insufficiency during a phase of stress and should be assessed and managed with expert opinion. Jaw ankylosis, atrophy of the masseter and other muscles of mastication, macroglossia and limited mobility of the cervical spine[6,11,12] categorize the patient as for management as difficult airway management. Ultrasound assisted peripheral cannulation may be needed for difficult intravenous access. With the patient being at a high risk of perioperative and post-operative complications post-operative ICU care should be arranged.

Peri-operative management

The most important issues in peri-operative and intra-operative management are the maintenance of the vital parameters, choosing the appropriate anesthetic agent and having a high index of suspicion to identify the possible rare complications. Patients should be meticulously monitored throughout the surgery with ECG, oxygen saturation, capnography and other standard monitoring as for any surgery. Invasive arterial blood pressure monitoring is recommended in potentially unstable patients.

Patients with neuromuscular disease are vulnerable to both hypothermia and hyperthermia. Reduced heat production and peripheral vasodilation of general and regional anesthesia predispose hypothermia. Normothermia should be ensured before induction and maintained using warm fluids and air warmers if needed. Exacerbation of myotonia, increased sensitivity to non-depolarizing neuromuscular blocking agents, rhabdomyolysis, bleeding and arrythmias are some of the life-threatening complications of hypothermia. Hyperthermia indicated by unexplained tachycardia, increased end tidal CO_2 concentration should be detected and treated aggressively. Patients with myotonias and muscular dystrophies should alert the team of the possibility of concomitant malignant hyperthermia.

Regional anesthesia is of advantage in patients with cardiac and respiratory impairment. However, they are best avoided in patients with rapidly progressive neurological deterioration in order to distinguish regional blockade from disease progression. Sympathetic blockade may aggravate autonomic dysfunction and necessitates the use of invasive monitoring and careful titration of hypotensive agents.

Use of volatile general anesthetic agents are controversial due to the association of malignant hyperthermia with some neuromuscular disorders such as Duchenne muscular dystrophy. Total intravenous anesthesia with a clean anesthetic machine are used to avoid rhabdomyolysis. Volatile agents are avoided as they cause cardiovascular decompensation due to cardiodepressive and arrhythmogenic properties. Total intravenous anesthetics are beneficial as they are short acting and relatively easy to control, however need caution due to the risk of autonomic dysfunction and cardiovascular collapse.

Neuromuscular blockade can be achieved by using depolarizing and non-depolarizing blocking agents but have to be used with caution. Depolarizing neuromuscular agents such as succinylcholine are not recommended as succinylcholine activates nicotinic acetylcholine receptors leading to an influx of cations into the sarcolemma, resulting in immobility of denervated muscles for prolonged periods. Further they increase the number of acetyl choline receptors throughout the muscle membrane and promote the development of fetal gamma isoform of the nicotinic acetylcholine receptor subunits. Acetylcholine activates both receptor groups leading to membrane depolarization and potentially massive potassium efflux which in turn causes fatal hyperkalemia, muscle fiber swelling and rhabdomyolysis. Fasciculations caused by succinylcholine may cause temporomandibular muscle spasm and may prevent intubation and ventilation in myotonias[1,13,14]. Interestingly myasthenia gravis patients are relatively resistant to succinylcholine and required dose may be increased up to two folds. Judicious use of total intravenous induction helps avoid non-depolarizing agents, since patients who are sensitive may develop respiratory weakness and difficult weaning, sputum retention and dysphagia. If a non-depolarizing neuromuscular agent is absolutely needed a 10 to 20% dose reduction is recommended with mivacurium and atracurium being the preferred agents due to their degradation process. Anticholinesterases cause hyperkalemia and are not recommended in muscle dystrophies.

Post-operative management

Patients with neuromuscular diseases are not suitable for day case surgery. They required planned elective surgery with planned admission and post-operative admission to high dependency or intensive care unit is mandatory. Institution of early and appropriate physiotherapy, positive pressure circuits and appropriate analgesics reduce post-operative complications. Post-operative pain and respiratory management play an important role in the outcome.

Pain management

Optimal pain control is of significant importance in patients with neuromuscular diseases and is achieved with preemptive analgesia and using multiple pharmacological agents. Hypoventilation secondary to splinting after thoracic, upper abdominal and spinal surgery can be prevented with adequate pain control[6]. Providing

adequate analgesia by titrating intravenous opioids helps airway clearance and minimizing respiratory suppression[6,11,12]. Post-operative analgesic requirements can be reduced by preoperative administration of clonidine or the use of intravenous paracetamol alone or in combination with non-steroidal anti-inflammatory agents[15,16]. Optimal analgesia with minimal respiratory side effects can be achieved by continuous infusion of opioids via epidural catheter when appropriate[17]. Wound infiltration with local anesthetics and continuous infusion of local anesthetics via a peripheral nerve block are safer alternatives. Peripheral nerve blocks provide comparable analgesia with less side effects compared with epidural[18]. Neuropathic deep pain and dysesthetic burning pain can be treated with gabapentin.

Respiratory management

Optimal management of post-operative respiratory management plays a crucial part in the recovery of the patient and depends on the pre-operative respiratory function and the type of surgery[6,11]. Those with normal cough clearance and relatively preserved muscle function are not at increased risk, while those with decreased respiratory function require close monitoring and aggressive management. Combination of non-invasive ventilation with mechanical insufflation and exsufflation after extubation of high risk patients reduce the need for reintubation or tracheostomy and shortens the ICU stay[11,19,20]. In patients with baseline FVC < 50% of predicted should be considered for extubation directly to non-invasive ventilation[6,11]. Subjects with preoperative peak cough flow (PCF) < 270 l/min or maximum expiratory pressure (MEP) < 60 cm H_2O should be supported with assist cough techniques[21].

Extubation must be delayed until respiratory secretions are well controlled and SpO_2 normal or baseline at room air[22]. Respiratory support must be continued in the post-operative period in patients requiring long term mechanical ventilation. In addition to correcting hypoxia, treating the underlying causes such as hypercapnia, mucus plugging, and atelectasis is important. CO_2 levels should be monitored to facilitate appropriate oxygen use.

Post-operative complications

Common post-operative complications include rhabdomyolysis, autonomic dysfunction, myotonias, cardiac and respiratory complications and malignant hyperthermia.

Rhabdomyolysis: Depolarizing neuromuscular blocking agents cause massive changes in ion distribution with muscle contraction, swelling and damage leading to rhabdomyolysis. Volatile agents may also cause malignant hyperthermia. Metabolic acidosis, hyperkalemia, myoglobinuria, creatinine kinase >10,000 U/L are suggestive of rhabdomyolysis and management includes cessation of the potential causative agent, correction of life-threatening hyperkalemia and maintaining a urine output of 1ml/kg/hour. Urine may be alkalinized using sodium bicarbonate. Dantrolene is used in the management of hyperthermia.

Autonomic dysfunction: Common in neuromuscular diseases may cause severe hypotension on induction and after regional anesthesia. It also causes gastric dysmotility leading to regurgitation and aspiration specially during general anesthesia. Sympathomimetic drugs should be available, and doses may need to be reduced due to increased sensitivity of alpha and beta receptors.

Myotonia: Myotonic contractures can occur in dystrophic and non-dystrophic myotonic disorders. Repeated action potentials lead to a permanent sodium influx or chloride efflux across the muscle membrane making it hyperexcitable. Drugs such as succinylcholine, anticholinesterases and opioids and environmental factors including alteration in temperature, acidosis and shivering trigger a contraction. If a myotonia is triggered they are not classically responsive to neuromuscular block, regional or peripheral nerve blocks. Management includes correction of environmental and physiological conditions and removal of the offending drug when possible. Drugs of choice in the management include drugs which block sodium channels such as local anesthetics and antiarrhythmic agents.

Cardiac complications: Cardiomyopathies and conduction abnormalities increase the morbidity and mortality. Perioperative catecholamine release precipitate arrythmias and potentiate cardiac failure. Patients should have acess to invasive monitoring, inotropic drugs and high level post-operative care.

Respiratory failure: This is the commonest cause of death in patients with neuromuscular diseases and also results in repeated aspiration (bulbar weakness), poor pharyngeal and respiratory muscle tone, obstructive sleep apnea and progressive spinal deformities leading to restrictive lung disease. Management includes extubation as early as possible to prevent further weakening of respiratory muscles. However, this needs to be weighed against the risk of atelectasis, aspiration, infection and respiratory failure.

Malignant hyperthermia: There is an increased risk of malignant hyperthermia during anesthesia. This may occur as a true malignant hyperthermia or a contracture related rhabdomyolysis and acidosis. Management has been discussed under rhabdomyolysis.

Conclusion

Patients with neuromuscular disease are at a high risk of intraoperative and postoperative complications and thus require a multidisciplinary team approach to be in place in the perioperative period. Surgery should be performed electively and only in hospitals which are fully equipped and with experience in managing patients with neuromuscular disorders. In emergency situations the essential lifesaving procedures should be performed and patient should be stabilized and transferred to a fully equipped hospital.

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Case report

Anti-MOG antibody associated recurrent optic neuritis

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Index words: optic neuritis, MOG, aquaporin-4, antibody, NMOSD

Introduction

Recurrent optic neuritis is associated with multiple sclerosis (MS) and neuromyelitis optica spectrum disorders (NMOSD)[1]. NMOSD is typically associated with recurrent attacks of optic neuritis and spinal cord involvement and seropositivity for aquaporin-4 antibodies; although some 10-40% remain AQP4 seronegative with NMOSD phenotype. Anti-MOG antibodies have a wider association with optic neuritis, transverse myelitis and encephalitis and is not limited to NMOSD. This distinct disease entity is proposed a new term, MOG-IgG-associated optic neuritis, encephalitis and myelitis (MONEM)[2,3]. We report a case of MOG antibody-associated recurrent optic neuritis that recurred after an unusually protracted interval.

Case report

A 30-year-old man presented with acute onset deterioration of vision in both eyes. The visual loss in the left eye developed over 12 hours and he noted that the vision was reduced to only finger counting. The vision loss was initially patchy, gradually progressing to complete loss of vision. There was no fever or constitutional symptoms. Six days prior to his presentation he had noticed subacute loss of vision in the right eye. He did not have intractable hiccups, vomiting or nausea. The patient did not complain of other neurological deficits. There was no history suggestive of connective tissue diseases.

In the year 2000, at the age of 13 years, he had been diagnosed with steroid sensitive bilateral optic neuritis. In 2005, at the age of 18 he had developed right-sided Bell palsy which had recovered with a short course of steroids and physiotherapy. The rest of his medical history was unremarkable.

On examination, the vision in the right eye was reduced to only perception of light while the visual acuity was 6/60 in the left eye. Fundal examination showed temporal pallor of the left optic disc and blurred margins of the right optic disc. Eye movements were full. Rest of the neurological examination was normal. His general and other system examinations were normal.

The full blood count, liver and renal profiles along with serum inflammatory markers were within normal limits. MRI of the brain and orbits with contrast, were normal. The cerebrospinal fluid analysis including the full report, pyogenic cultures and oligoclonal bands were negative. Serum was negative for aquaporin-4 antibodies and anti-nuclear antibodies. However, anti-MOG antibodies were detected in serum (cell-based assay, Euroimmun).

A diagnosis of anti-MOG antibodies-associated optic neuritis was made. He was treated with intravenous methylprednisolone 1 g daily, pulses continued for 5 days. On day 5 of treatment, his visual acuity had improved to 6/60 on the right and 6/36 on the left. Following intravenous steroid pulses, he was continued on oral prednisolone 1mg/kg/d while commencing on mycophenolate mofetil (MMF) 250 mg twice daily which was gradually titrated up to 1 g twice daily over the next 4 weeks. Prednisolone was tapered gradually over 4 weeks to 20 mg/d.

By the end of one month of treatment his visual acuity had improved to 6/12 in the right eye and 6/6 in the left eye.

Discussion

We report a case of recurrent of optic neuritis with MOG-antibody seropositvity that relapsed after a protracted interval of 17 years. The previous longest interval reported between two episodes of autoimmune optic neuritis is 14 years[4]. Recurrent optic neuritis is characteristic in multiple sclerosis, neuromyelitis optica spectrum disorders and anti-myelin oligodendrocyte glycoprotein (anti-MOG) associated neurological diseases[2].

Anti-MOG IgG is associated with a wide variety of clinical presentations, majority of which are optic neuritis, encephalitis with brain demyelination lesions and myelitis. However, of this wide spectrum of disorders associated with anti-MOG antibodies, only a third of patients fulfil the criteria for NMOSD. Out of the MOG Ig-associated phenotype spectrum the most prevalent is optic neuritis (41-60%) while combined optic neuritis and myelitis occur in only 6-24%[2]. Anti-MOG IgG is considered a unique biomarker of CNS demyelinating disease and is useful in differentiating it from multiple sclerosis[3].

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Myelin oligodendrocyte glycoproteins are a highly immunogenic component of the myelin sheath albeit accounting for less than 0.5% of its composition. Although the disease spectrum of MONEM and aquaporin IgG seropositive NMOSD overlap to a certain degree in clinical presentation, the pathological process has striking differences. In NMOSD, the primary pathology is the astrocyte damage due to the antibodies to aquaporin-4 protein resulting in a secondary loss of oligodendrocytes and demyelination. There is no astrocytopathy in MOG IgG-associated patients, where the pathology is primarily demyelination affecting oligodendrocytes, which predicts better prognosis and good recovery with the disease predominantly affecting the optic nerves.

The rate of relapse of optic neuritis is lower in MOG Ig-associated optic neuritis[5] than in NMOSD. Furthermore, the recovery from an episode of optic neuritis is better than in NMOSD and are at a lower risk of sustained visual impairment as one episode may result in less retinal neuronal loss in MONEM.

Treatment of MOG Ig-associated optic neuritis is with intravenous methylprednisolone, plasma exchange or intravenous immunoglobulin similar to other CNS immune-mediated conditions. Intravenous methylprednisolone followed by oral corticosteroid therapy has shown short-term benefit by accelerating the rate of recovery of vision[6,7]. However unlike in NMOSD, long-term management options with steroids and immune suppression has not been adequately studied. The monophasic nature and lower risk of relapse in MOG antibody-associated optic neuritis brings uncertainty in to the need for long-term therapy. The use of immunosuppressants may reduce the number of relapses[8]. In patients with relapse following acute treatment with steroids, use of intravenous immunoglobulins or mycophenolate mofetil (MMF) is the next option in treatment. Prolonged steroid taper is recommended as second line drugs such as MMF may take months to reach full efficacy[2].

The challenge in management of MOG antibody-associated disease is the long-term management. The need for therapy itself is a decision of uncertainty given the possibility of monophonic disease with good recovery. The relevance of persistence of MOG antibodies and its titres in predicting the necessity for long-term therapy remains unresolved[2].

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Case report

Varicella vasculopathy as a cause for stroke in a patient with diabetes – an uncommon cause for a common disorder

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Background

Varicella zoster is a humanotropic alpha herpes virus that causes two distinct diseases. The primary infection results in varicella (chickenpox). Then, the virus lies latent in the ganglionic neurons, becoming reactivated to cause herpes zoster when the host ages or becomes immunosuppressed.

It is estimated to cause neurologic complications in 1-3 per 10,000 cases[1]. Vascular disease following varicella infection encompasses a wide spectrum of presentations and arterial territory involvement – ranging from transient ischaemic attacks, acute strokes, aneurysms, subarachnoid and intracerebral haemorrhage, arterial ectasia and dissection, cerebral venous sinus thrombosis, spinal cord infarction, cranial neuropathy and peripheral arterial disease. A temporal arteritis mimicking giant cell arteritis has also been reported.

These can occur following either form of the infection, in both immune-competent and immune-compromised individuals. Though the exact incidence is unknown, several studies have indicated that there is an increased risk of stroke after varicella zoster[2].

Herein we report a female with stroke secondary to varicella vasculitis involving large intracranial vessels followed by a brief review of the literature.

Case report

A 67-year-old recently diagnosed diabetic woman presented seven weeks after acute onset painless left sided vision loss following herpes zoster of the left V2, T2, and T3 dermatomes a week prior. The left optic disc was pale, suggesting a late presentation of ischaemic optic neuropathy. She complained of memory impairment as well and was disoriented to time, but not to place or person. We also noted that she had a right sided hemiparesis with an MRC (Medical Research Council) scale of four with an extensor plantar on the right side though she did not specifically complain of weakness. The rest of her physical examination was normal.

Her inflammatory markers were normal, as were her full blood count, renal and liver functions. A left sided sub-acute haemorrhagic parieto-occipital infarct was seen on MR scan of the brain (Figure 1), with magnetic resonance angiography (MRA) showing absence of flow in the left internal carotid artery (ICA). The cerebrospinal fluid was haemorrhagic and showed high titres of anti varicella zoster IgG of 559.43 U/mL. Vasculitic screen including antinuclear antibodies, anti-neutrophil cytoplasmic antibodies and perinuclear neutrophil antibodies were negative. MR scan of the brain with black blood protocol failed to show vasculitic (intimal) changes which could be due to the late presentation.

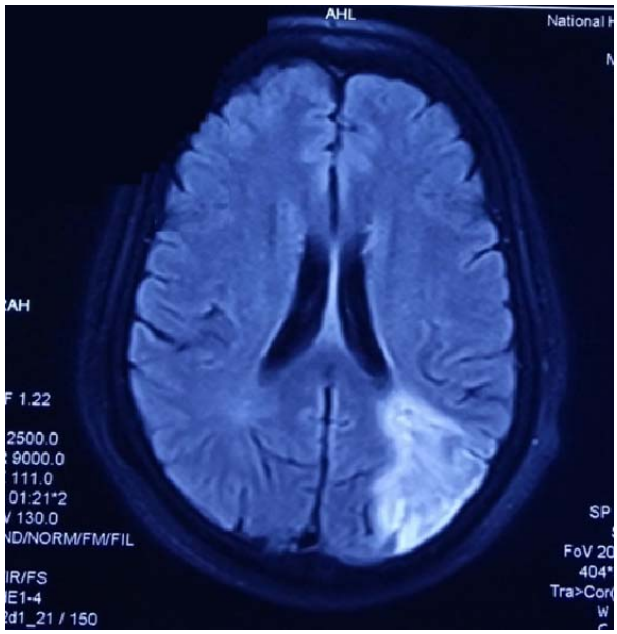

Figure 1. Subacute haemorrhagic left sided parieto-occipital infarct.

We treated her with a prolonged course of oral acyclovir and high doses of steroids following a presumptive diagnosis of varicella vasculopathy. However, though her clinical condition remained stable, her vision did not improve. A carotid doppler done two months later showed complete resolution of the thrombus with normal intima.

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Discussion

VZV (Varicella zoster virus) is thought to enter through the axons following either primary infection or reactivation to involve the cerebral arteries, which then undergo vascular remodeling resulting in thrombosis, dissections or aneurysms.

The presence of a multi-dermatomal rash suggestive of zoster within weeks of onset of the neurological symptoms, CSF pleocytosis and the presence of intrathecal production of varicella IgG in the CSF coupled with the presence of large artery involvement on imaging lends support to the diagnosis of varicella vasculitis in the above patient.

The infarct seen in our patient may represent an external (cortical) border zone or watershed infarct between the middle cerebral and posterior cerebral territory. Border zone infarction may be explained by invoking a combination of two often interrelated processes: hypoperfusion and embolization. Hypoperfusion, or decreased blood flow, is likely to impede the clearance (washout) of emboli in this case originating from the left internal carotid artery. This type of infarct occurs in 12.7% of all cerebral infarcts and may occur in situations involving severe systemic hypotension, such as when a person rises from the supine position, excess exercise, Valsalva's maneuvers, administration of antihypertensive drugs, bleeding, and anemia[3].

VZV causing strokes in adults has generally been described as a contralateral hemiplegia occurring weeks to months following herpes zoster of the ophthalmic division[4]. However, any arterial territory can be involved, and the manifestations can range from confusion and headache to hemi-sensory loss. A waxing and waning pattern is often recognised.

In a Taiwanese study, the risk of stroke increased by 30% within the following year in adults with zoster[2]. When zoster involved the ophthalmic distribution of the trigeminal nerve, the stroke risk increased 4.5 fold[2]. However it is important to note that in a study by Nagel et al.[5] one-third of patients with virologically verified VZV vasculopathy had no preceding rash.

Upon analysis of previously published reports of varicella vasculopathy causing ischaemic strokes in adults specifically (Table 1), at least half of those noted have been in immune-competent patients. A CSF pleocytosis can be an important pointer towards diagnosis especially in the absence of a rash, though this has been notably absent in cases six and seven, perhaps due to their immuno-compromised states.

A study of 30 subjects by Nagel et al. with virologically confirmed VZV vasculopathy[5] revealed a CSF pleocytosis in 67%. Haemorrhagic CSF can also be seen[6]. In nearly a third of the subjects in the above study, CSF contained VZV DNA. However anti-VZV IgG antibody was found in the CSF of 93% with reduced serum: CSF ratio of anti-VZV IgG confirming intrathecal antibody synthesis. Therefore detection of anti-VZV IgG antibody is considered a more sensitive diagnostic test compared to VZV DNA, since viral DNA is detected by polymerase chain reaction (PCR) in early disease and disappears late in the disease. VZV vasculopathy is often chronic and protracted and can occur on average four months after the rash which would make testing for anti VZV IgG more prudent. The longest period noted in the cases we have analyzed was six months. Intrathecal anti VZV IgG was detected in high titres in our patient which confirmed the diagnosis.

Brain imaging is abnormal in upto 97% cases of varicella vasculopathy[5]. MR scan of the brain may reveal superficial or deep, grey or white matter lesions – however lesions at the grey-white matter junction is considered more suggestive[7]. The lesions can also be haemorrhagic as seen in our patient. Angiographic abnormalities such as stenosis and occlusion were seen in upto 70%, with large and small arteries involved in 50%, small arteries only in 37% and large arteries only in 13%[4]. Any arterial territory can be involved. Multifocal involvement is also seen. The absence of angiographic abnormalities does not preclude the diagnosis, however normal brain imaging strongly argues against the diagnosis. Black blood MRI is a newer modality[8] that has been deemed useful though we did not demonstrate intimal changes in our patient.

A histopathological study of varicella vasculopathy suggested the presence of VZV antigen in the arterial adventitia in early VZV vasculopathy and in the media and intima of protracted cases of VZV vasculopathy. This supports the notion of virus persistence in the artery and spread from the "outside-in"[9]. The authors also demonstrated a thickened arterial intima composed of myofibroblasts and cells most likely of medial smooth muscle origin; a disrupted internal elastic lamina and a disrupted medial layer with a significant loss of normal smooth muscle cells. These changes help to explain why there is arterial occlusion and loss of vascular contractility, contributing to stroke.

Treatment of strokes due to varicella includes intravenous acyclovir for 14 days and oral prednisolone at 1mg/kg daily in immunocompetent patients, while those who are immunocompromised may need a longer course of antivirals[10]. Though our patient received oral acyclovir and steroids there was no clinical improvement. The treatment may have stabilized the course of her illness however.

Table 1.

Case	Age (Y)	Sex	Relevant underlying disorders	Rash	Rash to neurologic symptoms and signs	Neurologic symptoms and signs to virologic analysis	CSF pleocy-tosis	RBC in CSF	MRI/ CT focal lesions	Focal vascular abnor-malities	Artery involve-ment	CSF	VZV	Reduced serum/ CSF ratio of VZV IgG	Refer-ence
												DNA	IgG		
1	73	M	None	-	NA	4W	+	+	+	+	Large	NA	+	NA	(1)
2	54	M	AIDS	-	NA	3d	+	+	+	ND	Small	+	+	+	(2)
3	34	M	AIDS	+	6m	3w	+	+	+	ND	Small	-	+	+	(2)
4	42	M	None	-	NA	10-14d	+	-	+	+	Mixed	-	+	+	(3)
5	28	M	HIV, Hep C	-	NA	3 m	+	-	+	-	Mixed	+	+	+	(4)
6	71	M	Leukemia	+	1 m	6 m	-	+	+	+	Large	-	+	+	(5)
7	51	F	CREST syndrome	-	NA	2 m	-	+	+	+	Mixed	-	+	+	(6)
8	36	M	HIV	+	7 d	14 d	+	NA	+	+	Mixed	+	+	+	(7)
9	39	M	-	+	1 w	NA	+	NA	+	+	Large	-	-	ND	(8)
10	51	M	Glomerulo nephritis ǂ	+	2w	NA	+	NA	+	ND	NA	-	+	ND	(9)
11	61	M	-	+	4 w	NA	ND	NA	+	+	Small	ND	ND	ND	(10)
12	48	M	-	+	6 w	NA	ND	NA	+	+	Large	ND	ND	ND	(10)
13	55	F	-	+	6 w	NA	ND	NA	+	-	Small	ND	ND	ND	(10)
14	62	M	-	+	2 d	NA	ND	NA	+	+	Large	ND	ND	ND	(11)
15	67	F	DM	+	1w	8W	+	+	+	-	Mixed	ND	+	ND	Present case

Table redrawn from Nagel et al, with emphasis on cases that included ischaemic stroke as a presentation. Cases 1-10,15 are virologically proven definite cases of varicella vasculopathy. Cases 11-14 are of possible varicella vasculopathy.

Abbreviations: Y = Years, AIDS = Acquired Immunodeficiency syndrome, Hep C = Hepatitis C, CREST = Calcinosis, Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly, and telangiectasia, DM = Diabetes Mellitus, ND = Not done, NA = Not available, ǂ = Antineutrophilic cytoplasmic antibodies - associated pauciimmune glomerulonephritis.

In our patient, the stroke could have been attributed to her already existing vascular risk factor. However, the sequence of events in her clinical course led to the diagnosis of varicella vasculopathy as the eventual cause for stroke. This enabled us to extend her treatment options.

To complicate matters further, diabetes may be an independent risk factor for varicella vasculopathy even without a history of zoster infection in the past. In a study of cerebral arteries obtained from 4 subjects with diabetes and no history of zoster infection, transient ischemic attacks, stroke, or immunosuppression, less than 24 hours after they died, inflammation was found in the arterial adventitia in the temporal artery due to varicella with the presence of VZV DNA in one patient[11]. The authors concluded that it may be prudent to consider VZV vasculopathy as an additional cause of stroke in people with diabetes, particularly since it is treatable.

We believe a neurological event temporally related to a recent varicella zoster infection should alert the clinician to the possibility of varicella vasculopathy – especially in the absence of vascular risk factors and among immunocompromised individuals. Absence of the rash of zoster infection preceding the neurological

Box 1.

When to suspect varicella vasculopathy in a patient with stroke?

1. If a history of antecedent rash of varicella zoster is present in a patient presenting with stroke.
2. In the absence of a rash consider in an immuno-compromised state especially in the presence of diabetes.
3. If MR scan of brain demonstrates lesions in the grey-white matter junction or if lesions are haemorrhagic.
4. If an unusual sequence of neurological events occur with waxing and waning pattern.
5. CSF demonstrates pleocytosis or is haemorrhagic.

symptoms does not preclude a diagnosis of varicella vasculopathy. Diabetes may be an independent risk factor for varicella vasculopathy. In these cases, CSF pleocytosis and compatible brain imaging may be useful in making a definitive diagnosis (Box 1).

It is important to have a high index of suspicion and to be aware of important ancillary features in clinical presentation and brain imaging in varicella associated vasculopathy to aid in correct diagnosis.

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Case report

A treatable cause of fasciculations with upper motor signs

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Index words: lewis sumner syndrome, late onset conduction block, central and peripheral demyelination, plexus hypertrophy

Introduction

Patients with a lower motor neuron (LMN) syndrome characterized by weakness, wasting, diminished reflexes, fasciculations, cramps and minimal sensory involvement have a broad differential diagnosis. These include anterior horn cell disease (AHCD), Chronic inflammatory demyelinating polyneuropathy (CIDP), Multifocal Motor Neuropathy (MMN), Multifocal Acquired Demyelinating Sensory and Motor neuropathy (MADSAM) or Lewis Sumner Syndrome (LSS). Therefore an extensive electrophysiological search for inflammatory neuropathies is imperative to diagnose potentially treatable conditions.

LSS is a neuropathy characterized by asymmetric multifocal motor and sensory loss and conduction blocks (CB). Rarely peripheral nerve demyelinating diseases may be accompanied by CNS demyelination causing diagnostic confusion. The following case highlights the differential diagnosis and diagnostic pitfalls in diagnosing this rare electro-clinical syndrome that is highly treatable.

Case report

A 45-year-old man presented with a 3 weeks history of pain and weakness of the right arm. He complained of difficulty in lifting his arm, doing his buttons and persistent muscle twitching and cramps on the right. He was also unsteady on his feet. He was evaluated for a numb right foot two years ago and investigations with nerve conduction studies (NCS) revealed a diagnosis of 'length-dependent asymmetric sensory neuropathy'. Investigations for cause of neuropathy were normal.

Neurological examination revealed profuse fasciculation around right shoulder girdle and forearm muscles. There was hypertrophy of the biceps and distal wasting of forearm. Tone was normal. There was a 3-4 MRC grade weakness of deltoid, biceps, infraspinatus, finger extensors and finger flexors. No winging of scapula was detected. Reflexes were depressed on the right. There was no demonstrable sensory loss in the upper limbs. Localised tenderness over the right supra-clavicular area was noted without any lumps or lymph nodes. The right plantar had an extensor response on lower limb examination. The rest of the lower limbs, allowing for some patchy distal right sensory impairment were normal. The cranial nerves were normal. He was not ataxic but demonstrated impaired tandem gait.

The NCS of the lower limbs showed: absent sural (bilaterally) and superficial peroneal SNAPs on the right, normal lower limb motor responses and prolonged tibial F waves of 68ms. Upper limb nerve conduction velocity, F waves and SNAPs were normal. A partial motor Conduction Block (CB) in the upper limb (median nerve) was demonstrated when the study was repeated for the third time after 8 weeks. Compound muscle action potential (CMAP) was very low (0.2MV) and the distal motor latency (DML) was prolonged (10.8ms) over the right deltoid when stimulating over Erb's point. The needle EMG showed fasciculations (3+), in the right upper limb muscles and a few in the right tibialis anterior. No changes of acute denervation (fibs/ Positive Sharp Waves) were detected. The CSF showed elevated proteins (630mg/dl). The following results were normal; renal functions, blood count, ESR, CRP, liver functions, B12, folate, ANA, ANCA, HBA1C, protein electrophoresis, GM1 antibodies and cryoglobulins.

MRI cervical-spine showed no evidence of compressive radiculopathy. However there was focal high signal in the spinal cord at the level of C4. MRI of the brachial plexus showed thickened non-enhancing right C5/6 nerve roots. This abnormality extended through the brachial plexus further distally. No fat atrophy of shoulder girdle muscles was noted.

A trial of immunoglobulins made a significant improvement in disability within two weeks. However his arm became very weak after 4 months prompting a second course which resulted in a dramatic improvement in upper limb power to MRC 4+/5 within a week. The fasciculations of the arm and biceps hypertrophy had also resolved by this time.

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	DML (msec)	Amp (mV)	PML (msec)	Amp (mV)	CV (mmsec)	SNA (μV)	CV (mmsec)
1st study	4.1	4.5	9.9	4.0	46	5.6	58
2nd study	4.1	6.8	10.25	4.2	47	2.2	42
3rd study	3.4	4.2	9.35	2.1	47	-	-

PML – Proximal Motor Latency

AMP – Amplitude

CV – Conduction Velocity

SNAP – Sensory Nerve Action Potential

Figure 1. Electrophysiology parameters in consecutive studies of the right median nerve. The last study was done 8 weeks after the first. Arrows demonstrate partial CB.

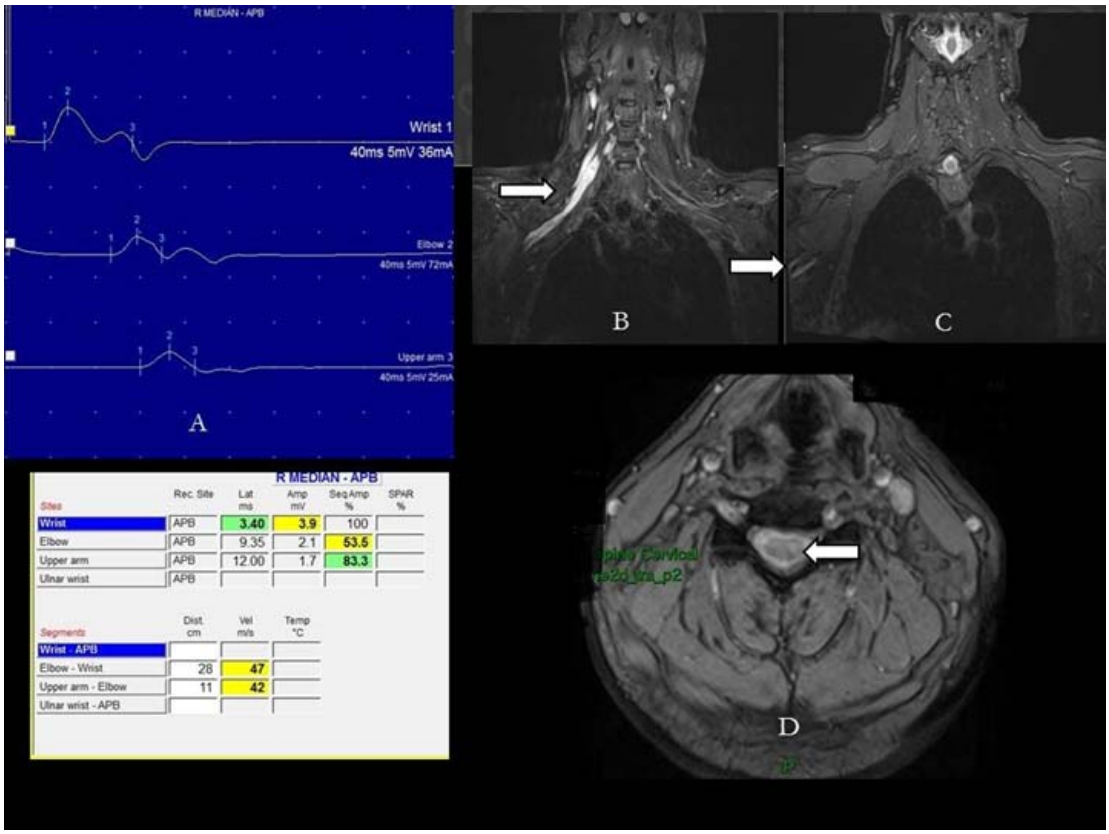

Figure 2.

A – Nerve conduction study demonstrating motor nerve conduction block over the elbow.

B – MRI STIR image demonstrating root hypertrophy involving C5, 6 and 7. MRI STIR image also shows hypertrophy of the right axillary nerve.

C – Spinal MRI – sagittal and axial sections showing focal demyelination a C4/C5 segment.

Discussion

AHCD, idiopathic brachial neuritis and mononeuritis multiplex (MNM) were considered initially in this patient. Needle EMG showed fasciculation's giving the impression of AHCD, however absence of denervation (ie:- fibs/ PSW) was against this diagnosis.

Acute shoulder pain with monoparesis is a common presentation for idiopathic brachial neuritis. EMG findings, notably absence of denervation potentials after 4 weeks makes brachial neuritis less likely in this patient. MNM is a painful, asymmetrical, sensory and motor peripheral neuropathy involving at least 2 nerves. However the presence of partial CB, prolonged F waves and the absence of NCS/ EMG features of asymmetric axonal neuropathy excludes MNM.

Our patient had slowly progressive markedly asymmetric multifocal neuropathy (lower limb prolonged F waves; absent SNAPs) with features of CB on NCS, elevated CSF protein absent anti-GM1 antibody (present in MMN) and thickened roots/plexus on MRI. These features strongly suggest a diagnosis of LSS. In chronic acquired demyelinating polyneuropathy, it is important to differentiate LSS from CIDP and MMN. In LSS, MMN, and CIDP, the NCS show features of demyelination, such as conduction block, temporal dispersion, prolonged distal motor latencies, slow conduction velocities, and absent or prolonged F-wave latencies in one or more motor nerves. LSS is different from MMN due to sensory nerve involvement and different from CIDP due to marked asymmetric multiple nerve involvement.

A series which compared LSS with MMN suggested that initial involvement was more frequent in upper limbs in MMN than LSS.[1] Motor weakness in the distribution of individual nerves was not different except for the median nerve, which was more frequently involved in LSS. F-waves were prolonged in the same proportion of patients with MMN as for LSS patients, but these abnormalities were more widespread in LSS. Sensory abnormalities were always absent with MMN and present in LSS. Our patient had initial lower limb involvement, F wave abnormalities, sensory findings and median nerve involvement which lent further support to the diagnosis.

It is unusual for LLS to present with focal muscular hypertrophy (FMH) which resolved along with fasciculations after treatment. It was postulated that severe fasciculations caused the muscle hypertrophy. This has been described previously.

Partial CB in this patient was diagnosed in the median nerve as CMAP amplitude and area decreased by 50% on proximal compared with distal stimulation, and CMAP duration increased by 30%. This is compliant with electro-diagnostic criteria. However caveats for the above, needs to be considered and include: over/under stimulation during the test and variations in anatomy of the median nerve (the first two NCS tests did not show any abnormality of the said nerve). The CB of the above patient was detected late in the course of the disease thus delaying the diagnosis. The delay is usually due to either less extensive electrophysiology or due to late onset CB. Lack of abnormal demyelinating findings in the distal limbs below the axilla or knee suggest that demyelination might have begun in the brachial or lumbar plexus in the early stage which might result in normal NCS of the peripheral nerves. CB found for the first time by stimulation at Erb's point has been described previously. In our case the CMAP of the deltoid was very low (<10% of expected normal) with significantly prolonged DML on stimulating Erb's point. However needle EMG did not demonstrate denervation changes; which suggests that this abnormality was due to proximal CB. Late onset CB with only F-waves being absent has been previously reported in LSS. Therefore it is suggested that repeated NCS should be undertaken to correctly diagnose LSS when it is suspected based on clinical symptoms with abnormal F-waves alone.

A confounder for the above diagnosis was an extensor plantar response suggesting an upper motor neuron (UMN) syndrome. Thus imaging of the CNS was performed in which we found an area of spinal cord demyelination. In a series which retrospectively investigated clinically and with MRI a cohort of patients with definite CIDP found 2 out of 12 patients with a clear clinical spinal cord syndrome and radiological findings compatible with spinal cord demyelination[2]. The neurophysiological profile of one patient was strongly suggestive of LSS. In both cases, clinical CNS dysfunction consisted of extensor plantar response. Our case showed only extensor plantar response which may reflect the restricted extent of the spinal lesion causing minimal dysfunction. The absence of exaggerated reflexes may have been due to concurrent neuropathy.

The MRI (T2 STIR sequence) also revealed a thickened right brachial plexus which has been reported in CIDP, MMN, hereditary neuropathy with liability to pressure palsies, hereditary demyelinating motor and sensory neuropathy, and neoplastic peripheral nerve infiltration. Enlargement of nerve roots/ plexus and hyperintensity demonstrates the local inflammatory process and oedema. Thus neuroimaging has become an increasingly useful tool in the diagnostic process of typical and atypical inflammatory neuropathy including LSS, CIDP and MMN especially when the electrophysiology is indeterminate.

This case emphasises importance of electrophysiology in diagnosing a very treatable inflammatory neuropathy with focus on extensive search for motor CB. Distal NCS may be normal during the initial course of the disease thus stressing the importance of stimulating proximally to improve sensitivity. When clinical suspicion is high repeated NCS testing is of value in detecting late onset CB, especially when considering the slow progression of the condition (it has been reported that the average time to diagnosis in LSS is 4.8 years). The presence of UMN signs in a patient with suspected LSS suggests concurrent CNS demyelination thus its presence should not preclude the diagnosis.

Key points:

- LSS is a highly treatable condition with LMN signs characterized by weakness, wasting, diminished reflexes, fasciculations cramps and minimal sensory signs.
- The presence of UMN signs in LSS suggests concurrent CNS demyelination.
- T2 STIR MRI imaging improves diagnostic yield of LSS.
- Distal electrophysiology may be normal during the initial course of LSS, stressing importance of stimulating proximally to improve sensitivity.
- Slow progression and late onset CB may delay diagnosis of LSS, emphasizing importance of repeated testing when clinical suspicion is high.

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Case report

Cerebellar type multiple system atrophy (MSA-C)

Harsha Gunasekara[1], Shyama Subasinghe[2], Buddhi Abeywickrama[3], Dinuka Warapitiya[4]

Sri Lanka Journal of Neurology, 2019, **6**, 25-27

Index words: multiple system atrophy, cerebellar disease

Introduction

Multiple system atrophy (MSA) is a neurodegenerative disease characterized by abnormal deposition of the protein α-synuclein in the central and peripheral autonomic nervous system (synucleinopathy). MSA is classified in to Parkinsonian (MSA-P) and Cerebellar (MSA-C) sub types, depending on the predominant motor manifestation. We report a patient with MSA-C with characteristic clinical and radiological features.

Case history

A 61 year old house wife gave a history of progressive unsteadiness of gait for 5 years. She was unable to walk unaided over the last 2 years. There was no history of tremor, postural dizziness or breathing disorders.

Examination revealed normal cognitive functions and intact cranial nerves. Gait was broad based and ataxic needing bilateral assistance to walk. Severely impaired coordination was noticed bilaterally, with a left predominance. She had mild bilateral rest tremor, rigidity and minimal hypokinesis. Her recumbent blood pressure was 112/81 mmHg and dropped to 79/63 after maintaining erect posture for 3 minutes.

Her routine laboratory haematological and biochemical investigations including thyroid functions were normal. Non-contrast CT scan of the brain showed marked cerebellar atrophy (Figure 1). MRI scan of the brain showed pontine and cerebellar atrophy with the characteristic cruciform pontine hyperintensity giving rise to the "hot cross bun" sign (Figure 2). Tilt study confirmed dysautonomia but was negative for vaso vagal syncope. Levodopa treatment did not improve her extra pyramidal manifestations.

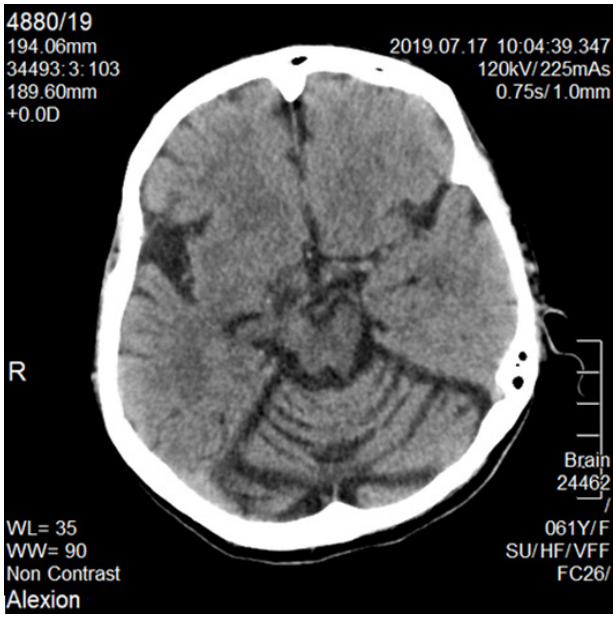

Figure 1. Non-contrast CT scan of the brain showing selective cerebellar atrophy.

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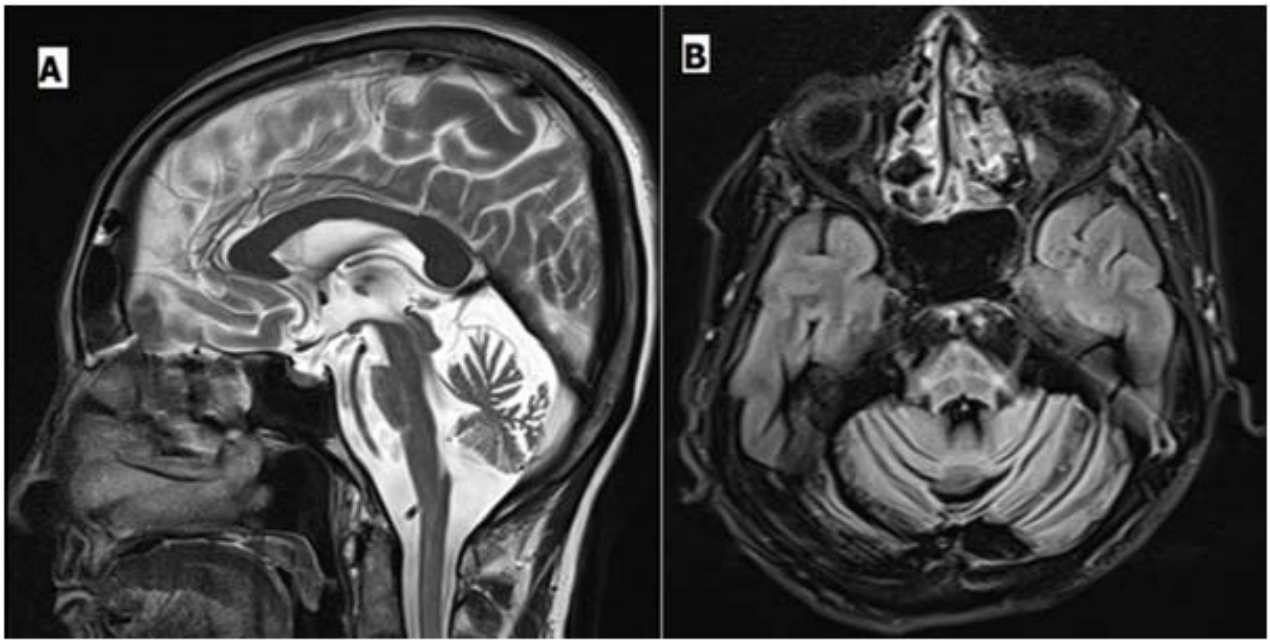

Figure 2. MRI brain T2 sagittal view showing pontine and cerebellar atrophy (A) and T2 axial FLAIR image view of the pons showing the "hot cross bun" sign (B).

Discussion

MSA is the most rapidly progressive synucleinopathy[1]. This patient satisfied the diagnostic criteria for probable MSA (Table 1). It is well recognised that patients with MSA have an initial phase of pure motor manifestation with an isolated Parkinsonism or cerebellar syndrome[3]. This can lead to a delay in the diagnosis. Isolated non-motor phase with pure autonomic failure is rare.

Radiological features are characteristic and aid the clinical diagnosis of MSA-C. These include selective atrophy of cerebellum, middle cerebellar peduncles and pons[4]. Selective loss of myelinated transverse ponto-cerebellar fibres and neurones in the pontine raphe with preservation of the pontine tegmentum and cerebral peduncles produce the "hot cross bun" sign. This sign may also be positive some sub types of Spino-Cerebellar Ataxia[4].

Table 1. Diagnostic criteria for probable multiple system atrophy[1]

Sporadic, progressive disease of adult onset (> 30 years old)
a) Autonomic failure involving urinary incontinence (inability to control the release of urine from the bladder with erectile dysfunction in males) or an orthostatic decrease of blood pressure within 3 min of standing by at least 30 mmHg systolic or 15 mmHg diastolic, ***and***
b) Poorly levodopa-responsive parkinsonism (bradykinesia with rigidity, tremor or postural instability), ***or***
c) A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia or cerebellar oculomotor dysfunction)

Conclusion

MSA should be suspected in any patient with otherwise unexplained cerebellar syndrome. Probable diagnosis of MSA could be made by careful evaluation of neurological status and autonomic functions. Characteristic MRI findings manifest early in patients with MSA-C than with alternative diagnoses.

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Point of view

Measles immunization in Sri Lanka; should it be changed for the prevention of neurological complications?

Jeevagan Vijayabala[1]

Sri Lanka Journal of Neurology, 2019, **6**, 28

Measles is a highly contagious infection caused by a paramyxovirus. Acute measles infection may be followed by potentially devastating central nervous system complications. These include acute encephalitis, acute disseminated encephalomyelitis and subacute sclerosisng panencephalitis (SSPE). SSPE is a fatal neurodegenerative disorder and develops several years after the acute measles infection.

Neurological complications are the major cause for measles related morbidity and mortality. Even though, introduction of measles vaccination resulted in substantial reduction in incidence of measles and related complications, still considerable amounts of cases are reported from developing countries. And Sri Lanka experienced two major measles outbreaks in the recent past. Furthermore, increasing number of SSPE are also reported in our country.

Traditionally, measles vaccine was given as combined MMR vaccine (Measles, Mumps & Rubella) at the age of one year and three years in Sri Lanka. However, the measles outbreak in 2013 made health care authorities to reconsider the traditional practice and currently MMR vaccine is given at 9 month and three years. Supplementary immunization with measles vaccine was given during major outbreaks.

One can learn many lessons from the latest measles outbreak. Majority of the cases were infants below one year of age. Of those infants, around 40% were between 9 to 11 months of age and almost 30% were aged between 6 to 9 months[1]. Even though, surveillance data on CNS complications of measles is lacking in our country, anecdotal evidence suggest those complications are on the rise.

It's plausible that substantial proportion of high risk infant less than 9 months are not protected by routine national immunization programme in Sri Lanka. It was thought that infants less than 9 months are protected by maternal immunity and vaccination before 9 months associated with increased numbers of vaccine failures. To the contrary, many studies suggested that at six months more than 90% of infants had lost the naturally acquired passive immunity from their mothers[2,3]. In addition, malnourished children in developing countries like Sri Lanka tend to loose maternally acquired antibodies sooner than their economically advantaged counterparts and are prone to acquire many infections at an early age.

At the same time, several studies assessed the impact of measles vaccination before 9 months of age. Notably, a clinical trial in in Guinea-Bissau revealed that measles vaccination in infants aged 4.5 months was safe and effective in producing adequate protective efficacy[4]. At 4.5 months merely 28% of enrolled infants had adequate level of maternal antibodies against measles. However, after early vaccination almost 92% had protective level of measles antibodies at 9 month of age. The number needed to treat to prevent single measles infection during 4.5 months to 9 months was 7.2. Furthermore, many developing countries recommend administrating MMR vaccine to infants 6 months through 11 months of age before international travel. It's also advised that infants who are vaccinated with MMR vaccine before their first birthday should be revaccinated with two more doses at least 28 days later.

In conclusion, the current MMR vaccination schedule in Sri Lanka, leaves infants less than nine months vulnerable to develop measles infection. I strongly suggest health care authorities to revisit the recommended age of first MMR vaccination and consider vaccinating at earlier age in order to reduce the gap in window of susceptibility. Whether first dose of MMR vaccine should be followed with one more dose or two more doses require a multicenter randomized controlled trial. Vaccination before 9 months of age will have a definite impact on CNS complications, since infants who develop measles at an earlier age are more susceptible for post infectious complications such as SSPE.

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[1]*Consultant Neurologist, Teaching Hospital Jaffna, Sri Lanka.*

Neurology quiz

Sri Lanka Journal of Neurology, 2019, **6**, 29-30

(Submitted by Manjula Caldera)[1]

1. What is the first US FDA approved treatment for Parkinson Disease Psychosis?

a. Clozapine
b. Quitiapine
c. Pimavanserine
d. Nusinersen
e. Haloperidole

2. Acute pandysautonomia is an acquired disorder with widespread but variable sympathetic, parasympathetic, and enteric autonomic dysfunction, including orthostatic hypotension, anhidrosis, unreactive pupils, decreased lacrimation and salivation, gastrointestinal paresis, and impaired genitourinary function.

What is the mostly recognized pathogenic Antibody?

3. (A) Who is this neurologist?

(B) What is this epic moment?

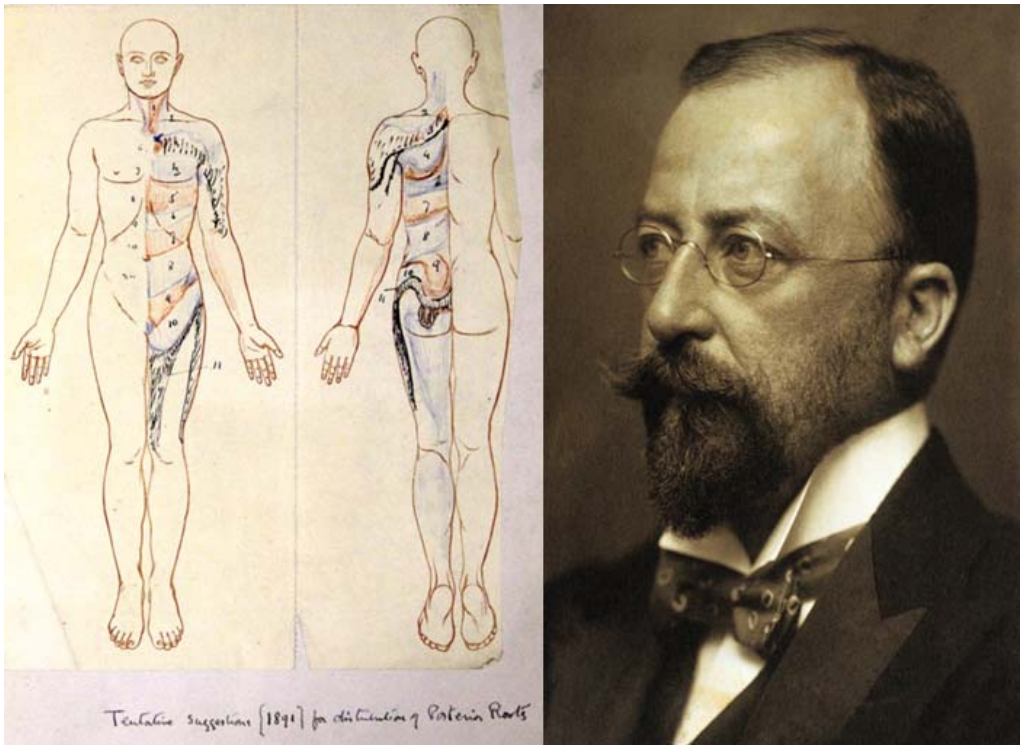
4. 60-year-old man as brought by his wife who reports that he has significant parasomnias with noisy breathing later confirmed to be stridor. Six months later had recurrent falls with drooling of saliva. Examination revealed supra nuclear gaze palsy with Parkinsonism.

What is the most likely diagnosis?

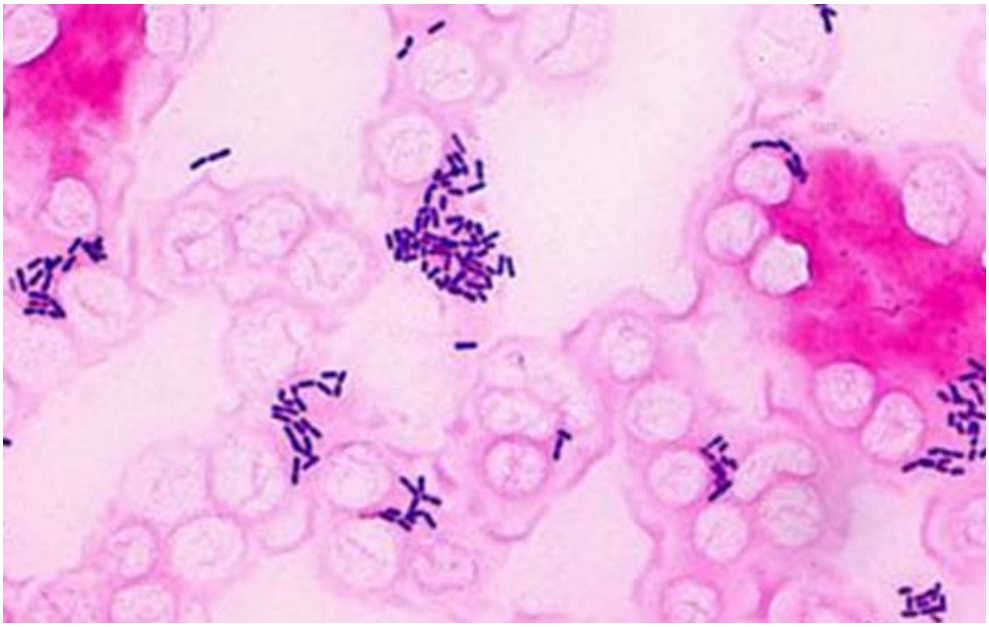
b. Multi System atrophy
c. DPPX Antibody associated encephalitis
d. Anti-IgLON5 disease
e. Mid brain tumor

[1]*Consultant Neurologist.*

5. Sir Henry Head was instrumental in describing dermatomal distribution of human body. Which infection did he study in depth to derive the dermatomal pattern?



6. Ingestion of food products is the most likely to be the mode of contracting meningitis of the following bacterium. Name the bacterium which is shown in the following gram-stain.



(Answers on page 34)

Guidelines to authors

Sri Lanka Journal of Neurology, 2019, **6**, 31-33

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Submit an original copy and 3 copies (photocopies are acceptable) of all parts of the manuscript, 3 original glossy prints of all figures. All submissions must be accom-panied by an electronic copy of the manuscript and illustrations emailed to the editor.

The manuscript should be mailed, with adequate protection for figures, to Prof Saman Gunatilake, the Editor, *SLJN*, Department of Medicine, Faculty of Medical Sciences, University of Sri Jayewardenepura, Nugegoda. SRI LANKA. Email: saman.gunatilake@hotmail.com

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1. Conceived and planned the work that led to the paper, or interpreted the evidence it presents, or both.
2. Wrote the paper or reviewed successive versions, and took part in revising them.
3. Approved the final version.
4. Each author should have contributed sufficiently to the work to take public responsibility for the content.

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In the cover letter give full details on any possible previous publication of any content of the paper. eg.

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Referees are asked to treat papers as confidential communications and not to share their content with anyone except colleagues they have asked to assist them in reviewing, or not to use content for their own purposes. They are asked to declare any conflict of interest (such as personal ties to authors), and not to copy manuscripts.

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All parts of manuscript, including tables and figure legends, must be typed with double-spacing. References must also be double spaced. Manuscripts should be typed in capital and lower case letters, on white paper, 216 × 279 mm (8 × 11 in), or A4 (212 × 297 mm). Arrange components in the following order: title page, abstract, text, references, tables in numerical sequence, and figure legends. Begin each component on a separate page. Number all pages consecutively, starting with the title page.

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The title page should contain the following:

1. Main title, subtitle (if any) and a maximum of 5 index words (or phrases).
2. Authors listed in the form and order in which they are to appear in the published article.
3. Institutional affiliation for each author, in a footnote on the title page of the article. The institutions listed should reflect the affiliations of the authors at the time of the study, not their present affiliations, if they differ.
4. Financial support information. Include the grant number, if any, and the granting agency. Other financial support, such as that for equipment and drugs, should also be listed.
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6. The number of words in the manuscript, exclusive of the abstract, references, tables, figures, and figure legends.

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Abstracts for articles are limited to 250 words; those for Brief Reports, to 150 words. Authors of original research articles are asked to submit a structured abstract organised into the following categories (where relevant):

Objective(s)

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Patients Intervention (if any)

Measurements

Results

Interpretation

Authors are asked to see papers in any recent issue of the *British Medical Journal or Annals of Internal Medicine* for guidance on structuring the abstract.

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Use only three levels of headings in the text. Clearly indicate the levels of headings by using different typographic conventions (such as all capital letters or bold type) or by positioning (flush to margin, indented). Keep headings short (three or four words).

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The *British Medical Journal, Lancet* and *Annals of Internal Medicine* are recommended to authors as guides to style, clarity of presentation and conciseness.

Units

Use SI units throughout [2], except for systemic arterial blood pressure and haemoglobin content. Other units may be given in parentheses. Use only arabic numbers.

Name of drugs and instruments

Generic names must be used for all drugs. Include the proprietary name only if it is needed for a specific purpose. Instruments may be referred to by proprietary

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Number references in the order in which they are first cited in the text. Use superscripted arabic numerals in the text.. Note that the *SLJN* requires the COMPLETE name of journal (and not its abbreviation), year, volume and first and last page numbers.

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2. Corporate author.

   The Royal Marsden Hospital Bone Marrow Transplantation Team. Failure of syngeneic bone marrow graft without preconditioning in posthepatitis marrow aplasia. *Lancet* 1977; **2**: 242-4.

3. Special format.

   Cahal DA. Methyldopa and haemolytic anaemia (Letter). *Lancet* 1975; **1**: 201.

Books: List all authors or editors when 4 or fewer; when 5 or more, list only the first 3 and add et al.

1. Author.

   Eisen HN. Immunology: *An introduction to molecular and Cellular Principles of the Immune Response*. 5th ed. New York: Harper and Row,1974.

2. Editors.

   Dausset J. Colombani J, eds. *Histocompatibility Testing* 1972. Copenhagen: Munksgaard, 1973.

3. Chapter in a book.

   Hellstrom I, Helstrom KE. Lymphocyte-mediated cytotoxic reactions and blocking serum factors in tumor-bearing individuals. In: Brent L, Holbrow J, eds. *Progress in immunology* II. v. 5. New York: American Elsevier, 1974: 147-57.

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1. In press (must have journal title).

   Dienstage JL. Experimental infection in chimpanzees with hepatitis A virus. *Journal of Infectious Diseases* 1975. In press.

2. Magazine article.

   Roueche B. Annals of medicine: the Santa Claus culture. *The New Yorker* 1971. Sep 4: 66-81.

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1. Personal communication.
   (Strott CA, Nugent CA. Personal communication).

2. Unpublished papers.

   (Lerner RA, Dixon FJ. The induction of acute glomerulonephritis in rats. In preparation). (Smith J. New agents for cancer chemotherapy. Presented at the Third Annual Meeting of the American Cancer Society, June 13, 1983, New York).

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All tables must be typed double-spaced. Tables should be numbered with arabic numerals, in the order in which they are cited in the text. A table title should describe concisely the content of the table.

Figures

Figures should be professionally drawn or prepared using a computer and high-resolution printer. Lettering should be uniform in style. Free hand or typewritten lettering is not acceptable. Number the figures in the order in which they are cited in the text. Photomicrographs should have scale markers that indicate the degree of magnification. Submit three glossy prints of each figure. Indicate on a label the name of the first author of the paper, the figure number, and the top of the figure: then paste the label on the back of the figure. Do not mount figures on backing board.

Colour figures may be submitted and will be published if essential.

Legends for figures

Reduce the length of legends by using partial sentences. Explain all abbreviations and symbols on the figure, even if they are explained in the text. Stain and magnification should be given at the end of the legend for each part of the figure. If there is no scale marker on the figure, the original magnification used during the observation should be given, not that of the photographic print.

Acknowledgements

Acknowledge only persons who have contributed to the scientific content and provided financial or technical support. Authors must submit written permission from persons acknowledged for other than financial or technical support.

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1. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. *New England Journal of Medicine* 1991; **324**: 424–8.
2. Young D. Implementation of SI units for clinical laboratory data: style specifications and conversion tables. *Annals of Internal Medicine* 1987; **106**: 114–29.

Answers to neurology quiz

Sri Lanka Journal of Neurology, 2019, **6**, 34

Answer 1

Pimavanserin (Nuplazid) is the first FDA-approved drug indicated for PD-associated psychosis (PDP). It does not induce clinically significant antagonism of dopaminergic, adrenergic, histaminergic, or muscarinic receptors. Although Clozapine and Quitiapine used in PDP they are off label drugs. Haloperidone has significant extrapyramidal side effects and Nusinersen is a novel drug used in spinal muscular atrophy.

Answer 2

Nicotinic ganglionic acetylcholine receptor antibody (nAChR)

The frequent association of high titers nAChR Antibody and/or paraneoplastic antibodies has suggested the etiology of acute pan dysautonomia is an immune mediated condition.

Answer 3

(A) Sir Roger Bannister

(B) Sub-4-minute mile

Before Bannister breaking this record, a four-minute mile was thought to be impossible. Sir Roger achieved this on 6th May 1954 at Oxford University's Iffley Road Track, with the help of fellow-runners Chris Chataway and Chris Brasher as pacemakers

Answer 4

Anti IgLON5 disease

Anti IgLON5 disease is a spectrum of disorders, which may present as sleep disorders (such as parasomnias and sleep breathing difficulty), a bulbar syndrome, a PSP like syndrome or cognitive decline with or without chorea. REM Sleep Behavioral Disorders (RBD) are not common in PSP (Steele-Richardson-Olszewski syndrome) which is a taupathy. MSA usually present relatively younger in age. DPPX antibody associated encephalitis is usually preceded by diarrhea, other gastrointestinal symptoms and weight loss.

Answer 5

Herpez Zoster

Answer 6

Listeria monocytogenes

Meningitic bacteria such as pneumococcal, meningococcal, haemophilus are acquired through nasopharyngeal route. Staphylococci through haematogenous and by trauma.

This gram stain report show a gram-positive bacilli. There are very few gram positive bacilli which could be classified as spore baring and non spore baring.

Spore bearing: Bacillus and Clostridium

Non spore bearing: Corynebacterium and Listeria