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AIMS AND SCOPE

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Editorial

Neurologic disorders and COVID-19

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SARS-CoV-2 with its wide range of disease severity ranging from asymptomatic carriers to severe respiratory compromise and death, is still with us. High rates of infection and subsequent long-term sequelae have raised significant concerns, particularly for those with underlying medical illnesses, who may be more severely affected. This includes not only those treated with immunosuppressive therapies for their neurologic disorders (e.g., myasthenia gravis or multiple sclerosis [MS]) but also those with significant functional disability from their disease and elderly patients with a history of cerebrovascular disease, Parkinson disease and dementia. As neurologic disorders are common, the effect of SARS-CoV-2 on patients with neurologic illnesses poses a substantial public health risk. Prioritizing this population is critical when considering the risks and benefits of vaccination.

The approval of vaccines for emergency use results in the potential to significantly reduce the incidence of symptomatic disease in these vulnerable populations. However, the rapidity of approval, and history of prior vaccination regimens resulting in neurologic and other complications, creates concern surrounding widespread vaccination.

The potential for neurologic complications is a concern, particularly for those who already have neurologic disorders. Neurologic complications have been reported in 30%-60% of patients with COVID-19 and typically fall into 3 broad categories: those that are caused acutely by the virus' systemic effects on the body itself, those that result from direct invasion of the nervous system, and those with long-term sequelae after an individual has recovered from the acute illness. Although there is no clear evidence at present that those with pre-existing neurologic illness are at higher risk of infection or neurologic complications, the question of whether individuals with neuromuscular or bulbar weakness may be more vulnerable to neurologic sequelae will require careful study.

Prevalence data on acute neurologic effects of COVID-19 are limited. In an article published in JAMA Neurology detailing 214 COVID-19-positive patients hospitalized in Wuhan, China, headache and dizziness were the most commonly reported neurologic complaints and seen early after symptom onset. These early symptoms contrast with the encephalopathy seen days to weeks into the hospital course of patients with severe disease. Encephalitis has been reported, mainly in a series of case reports[1], although imaging and CSF profiles have been nonspecifically abnormal or nonrevealing[3].

Evidence is largely lacking for direct CNS invasion of SARS-CoV-2 as a primary cause of neurologic sequelae. Several studies have detected low viral loads in brain tissue using quantitative real-time polymerase chain reaction (qRTPCR), but the clinical significance of these findings is uncertain. For instance, a recent autopsy study of 41 consecutive patients who died of SARS-CoV-2 infection found low to very low viral RNA levels in some of the brains by qRTPCR, but viral proteins were not detected, and the level of detectable RNA did not correlate with histopathologic alterations[4]. Other studies have not been able to detect viral RNA or protein in the brain. The virus does infect the sustenacular cells of the nasal mucosa, causing inflammation that causes loss of smell and headache. Similar systemic inflammatory effects of the virus might cause altered mental status in patients either directly or through an inflammatory cascade leading to cardiac or respiratory compromise with hypoxia or thrombosis. CNS effects have also been hypothesized to be caused by damage to vascular endothelium or blood-brain barrier breakdown. There have been case reports suggesting increased risk of large vessel occlusion and ischemic stroke associated with infection in the young[5]. It is also possible that the virus triggers underlying neurologic disease through immunomodulation as there have been case reports of acute inflammatory demyelinating polyneuropathy (AIDP), acute myoclonus, acute cerebellitis with ataxia, encephalitis, and status epilepticus occurring as para- or post-in-fectious phenomena. **In this issue there are two case reports one of a sciatic neuropathy following severe COVID-19 and the other of vaccine induced thrombo-cytopenia and cerebral venous thrombosis with extensive intracerebral haemorrhage**.

Long-term sequelae have been reported following previous viral epidemics; however, clear evidence linking specific complications to prior viral infection remains somewhat controversial and does not appear related to a single mechanism of action. The 1918 H1N1 pandemic's association with postencephalitic parkinsonism (PEP) and Zika virus-induced congenital Zika syndrome are examples. PEP is associated with encephalitis lethargica (von Economo encephalitis). Although encephalitis

lethargica has been associated with the H1N1 epidemic, this association has been challenged. Unlike the putative post-infectious autoimmune etiology of PEP, Zika syndrome is in large part the direct result of acute infectious injury to developing brain. Any report of long-term neurologic sequelae of COVID-19 will require careful analysis to demonstrate the validity of the association. Reports of long-term neurologic sequelae after recovery from COVID-19 have begun to be reported, and thus far include dysautonomia, chronic fatigue, and cognitive impairment[6]. with time it will be possible to fully characterize these issues and estimate their incidence. Patient registries will be crucial for determining whether SARS-CoV-2 infection, like other viral infections, will be associated with increased incidence of psychiatric disease, dementia, thrombosis, or demyelination later in life. **It is to the credit of the ASN that we already have such a registry where all Neurologists feed in their patient data on COVID-19 and vaccine related complications.**

Some literature supports the indirect effect of viral infections on those with neurologic disorders. Along with potentially triggering disease, there is an increased risk of mortality in patients with pre-existing neuromuscular illness who contracted influenza or pneumococcal pneumonia due to worsening respiratory status. Exacerbations of symptoms are commonly associated with infections, with infection accounting for almost half of patients presenting with myasthenia gravis flares. Viral infections are a common cause of transient worsening of existing symptoms in people with MS, and increased disability has been identified as a risk factor for severe COVID-19 in patients with MS. Viral illnesses can be a predisposing factor for delirium in patients with dementia or mild cognitive impairment, leading to poor prognosis. In addition, those on immunomodulating therapy are at risk for more severe, recurrent, and persistent infection.

COVID-19 has had profound effects on our health care system. The pandemic has been linked to decreased hospitalizations for those with ischemic stroke and other neurologic illnesses[7], resulting in poor access to care and increased burden of undiagnosed and untreated ischemic disease. **During the peak of the epidemic ASN members joined hands with the Sri Lanka Medical Association and Ceylon College of Physicians in the frontline. A high dependency unit was started for COVID patients in the Neurology Institute under the supervision of Neurologists. The ASN using their funds donated a transportable ventilator worth around two million rupees to the MICU of the National Hospital. Our members participated in educational programmes online for the public and healthcare staff.**

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Review

Fronto temporal dementias

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Abstract

Frontotemporal dementias (FTD) are a heterogenous group of neurocognitive disorders which varies with regard to their clinical presentation, radiological characteristics, pathology and genetics. The core FTD clinical syndromes are behavioural variant FTD (bvFTD), semantic variant primary progressive aphasia (svPPA) and non-fluent/agrammatic variant of primary progressive aphasia (nfvPPA). FTD related syndromes include frontotemporal dementia with motor neuron disease (FTD-MND), progressive supranuclear palsy syndrome (PSP-S) and corticobasal syndrome (CBS). This article discusses the clinical presentation, diagnosis, neuropathology, neurogenetics and therapeutics of FTDs.

Key words: frontotemporal dementia, primary progressive aphasia, behavioural variant frontotemporal dementia, semantic variant primary progressive aphasia, nonfluent/agrammatic variant primary progressive aphasia, motor neurone disease, progressive supranuclear palsy, corticobasal syndrome

Introduction

Frontotemporal dementias (FTD) are a diverse group of neurocognitive disorders which varies according to their clinical presentation, neuroradiological features, neuropathology and neurogenetics. The current understanding of this spectrum of disorders encompasses three core clinical syndromes; behavioural variant FTD (bvFTD), nonfluent/agrammatic variant primary progressive aphasia (nfvPPA), and semantic variant PPA (svPPA). In addition, there are disorders such as frontotemporal dementia associated with motor neurone disease (FTD-MND), corticobasal syndrome (CBS) and progressive supranuclear palsy (PSP-S), which are categorised as FTD related disorders. In this review, it is also discussed the various pathologies which are categorised under Fronto Temporal Lobar Degeneration (FTLD), genetics and therapeutics.

In 1892, Arnold Pick described a patient with progressive language dysfunction with temporal lobe atrophy in autopsy studies. In the pre brain imaging era, this is the first reported case of FTD[1]. In Pick's cases, Alois Alzheimer demonstrated interneuronal silver staining argyrophilic cytoplasmic inclusions in 1911[2]. They were later known as Pick Bodies. Further developments in clinical understanding, pathology and genetics over a century and especially the last three decades, lead to characterise our current understanding of the FTDs.

Epidemiology

While Alzheimer Disease is the most common type of dementia, FTD is the second most common cause in below 65 years[3]. In the USA, FTD prevalence ranges from 15-22 per 100,000 in the 45-65 years age group, with incidence ranges from 2.7-4.1 per 100,000[4]. This may be underestimating the actual figures, mostly due to under recognition of the condition or attributing it to other clinical conditions mostly as psychiatric disorders.

Behavioural Variant Frontotemporal Dementia

bvFTD is the commonest FTD, which characterises by the initial clinical presentations such as behavioural, emotional, personality and executive dysfunction[5]. They may develop symptoms such as disinhibition, apathy, lack of empathy and dietary changes[6]. These presentations are very likely to mistaken for a psychiatric illness. There are key six categories of symptoms (disinhibition, apathy, lack of empathy, compulsions, hyperorality and executive dysfunction) in diagnosing bvFTD. At least three should be present in order to make a possible bvFTD diagnosis[5] (Table 1).

Disinhibition could manifest as inappropriate behaviour such as overfamiliarity with strangers, inappropriate touching, and disrespecting interpersonal space. They may show impulsive behaviours like new onset gambling or excessive online shopping. Loss of manners or social decorum such as inappropriate comments or jokes to strangers, using rude language without embarrassment are commonly seen[6]. Behavioural disinhibition is linked to degeneration of the right orbitofrontal cortex[7].

Apathy or inertia could manifest as lack of involvement in family or social interactions, reduce drive to move, reduce social conversation or required frequent prompting from others. This could be easily misdiagnosed as depression[6]. Apathy in bvFTD has been correlated with degeneration of the medial prefrontal lobes and anterior cingulate cortex[8].

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Table 1. Diagnostic Criteria for behavioural variant FTD

(Adopted from Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*. 2011)[5]

I	Neurodegenerative disease	
	A	Shows progressive deterioration of cognition/behaviour by observation or history
II	Possible bvFTD: 3 of 6 must be present	
	1	Behavioural disinhibition
	2	Apathy/inertia
	3	Loss of sympathy or empathy
	4	Perseverative, stereotyped or compulsive/ritualistic behaviour
	5	Hyperorality and dietary changes
	6	Executive dysfunction with relative sparing of episodic memory and visuospatial function
III	Probable bvFTD; All (A-C) must be present	
	A	Meets criteria for possible bvFTD
	B	Exhibits significant functional decline
	C	Imaging results consistent with bvFTD
IV	Behavioural variant FTD with definite FTLD Pathology	

Lack of empathy or sympathy is common in bvFTD. These symptoms may especially be noticeable in the sorrowful events of the loved ones. Another aspect of bvFTD may be that the patient may not be concern of the impact and consequences of their diagnosis of bvFTD to others (frontal anosodiaphoria)[9]. Lack of empathy has been correlated with degeneration of subcallosal gyrus in bvFTD and right temporal lobe in svPPA[10].

Perseveration or stereotypies could be simple repetitive actions like tapping, lip smacking or more complex actions like collecting usually uninterested things which otherwise would end up in trash bin, walking repeatedly in same routes or counting rituals. Perseveration and stereotypies in bvFTD reported to be associate with degeneration in several brain areas[6].

Hyperorality and dietary habits could manifest as developing a sweet tooth, overeating and weight gain. Later in bvFTD, hyperorality may complicate with oral exploration which may end up with eating inedible things. Hyperorality has been strongly correlated with orbital frontal cortex, striatum and right insular cortex[11].

Executive dysfunction in bvFTD should be differentiated from Alzheimer disease. Presence of episodic memory and visuospatial function are useful markers in favour of bvFTD. Executive dysfunction in bvFTD could manifest as poor performances in jobs, unsuccessful investments or poor planning. Dysexecutive syndrome is strongly related to dysfunction of dorsolateral prefrontal cortex[12].

Neurocognitive assessment of bvFTD could initially be normal and a strong index of suspicion is required. Mostly the initial clues to the diagnosis would be gathered from the informant's history or by observation. Atrophy of the frontal and/or anterior temporal lobes in MRI/CT or hypometabolism in PET/SPECT would support a probable diagnosis of bvFTD[5].

Primary Progressive Aphasias

In PPAs the language dysfunction is the first symptom to be noticeable. Ninety years after Arnold Pick described the language dysfunction with temporal degeneration, Mesulam coined the term "slowly progressive aphasia" in 1982[13]. He renamed the disorder as primary progressive aphasia later in 1987[14]. There after PPAs were categorised as semantic dementias and progressive non fluent aphasias (PNFA) with some incomplete fitting for "fluent speech disorders with frequent word finding pauses" for nearly two decades until, Gorno-Tempini et al introduced the logopenic variant primary progressive aphasia (lvPPA)[15,16]. Since lvPPA is primarily associated with AD pathology[17], a detailed discussion is not intended in this review (See Table 3).

Semantic Variant Primary Progressive Aphasia

Temporal variants of the FTD spectrum of disorders expands our understanding of the language, behaviour and their neuroanatomical lateralisation. Semantic variant primary progressive aphasia (svPPA) presents with initial symptoms predominantly related to deficits of semantic knowledge. svPPA is about one fourth of FTDs[18]. About 70% of the patients who have predominant left temporal lobe involvement do usually present with semantic deficits. The remaining 30% which have right temporal lobe involvement presents with more behavioural symptoms[19]. Eventually both temporal lobes would get affected and result in an overlap syndrome.

The classic left temporal svPPA is also called as semantic dementia, presents with anomia and problems with single world comprehension[16]. While anomia is not specific for semantic dementia, it is more commonly seen in this variant. Word comprehension problems are initially common for low frequency words (giraffe) than frequently used words (dog). With disease progression, svPPA patients use categorical words (animal instead of dog, vegetable instead of carrot) and later may use very non-specific words (thing/place) more frequently. Semantic dementia patients find it difficult to read and write irregularly spelled words due to the loss of knowledge of that word. They may write "*det*" for debt and pronounce debt as "*deBt*". This phenomenon is named as surface dysgraphia and surface dyslexia respectively[16] (see Table 2).

Right temporal svPPA patients present with behavioural changes such as social isolation, irritability, compulsions[6,19]. They may fail to respond to social cues or facial expressions due to atrophy of right amygdala which is linked with the failure of recognizing the facial emotions[21]. With progression, they lose the ability of facial recognition (prosopagnosia) and eventually may fail to recognise themselves in front of the mirror.

It is interesting that svPPA patients may acquire new artistic abilities after development of their cognitive symptoms. Left temporal variant would develop new visual abilities like painting, while right temporal variant would acquire new writing abilities. But these skills would decline with the involvement of contralateral temporal lobe[6].

Table 2. Diagnosis of semantic dementia

(Adopted from Gorno-Tempini ML, Hillis AE, Weintraub S, et al. Classification of primary progressive aphasia and its variants. *Neurology.* 2011)[16]

Clinical diagnosis of svPPA	
A. Both of the core features should be present	
	1. Impaired confrontational naming 2. Impaired single word comprehension
B. 3 of the following 4 should be present	
	1. Impaired object knowledge (esp. for low frequency words) 2. Surface dyslexia or dysgraphia 3. Spared repetition 4. Spared speech production (grammar and motor speech)
Imaging supported svPPA	
A. Clinical diagnosis of svPPA +	
B. Imaging confirmation of at least one of the following	
	1. Predominant anterior temporal lobe atrophy 2. Predominant anterior temporal hypoperfusion/hypometabolism on SPECT/PET
svPPA with definite pathology	
A. Clinical diagnosis of svPPA+	
B. With one of the following must be present	
	1. Histopathologic confirmation of specific pathology 2. Presence of a known pathologic genetic mutation

Table 3. Differentiation of primary progressive aphasias

	svPPA	*nfvPPA*	*lvPPA*
Single word comprehension	lost	intact	intact
Grammar	intact	+/- lost	intact
Fluency	intact	lost	+/-lost (word finding difficulty)
Repetition	intact	affected	affected
Praxis of speech	intact	affected	+/- affected (Phonologic paraphasic errors)

Nonfluent/agrammatic Primary Progressive Aphasia (nfvPPA)

These patients present with initial symptoms of effortful speech and word finding difficulties. With disease progression, the speech become slower and more effortful. They make inconsistent errors of phonation with insertions, deletions and distortions of sounds. This could be appreciated by asking to repeat a complex structured word (hippopotamus, catastrophe). Agrammatism may be absent or subtle initially and may affect in the later stages. Aphemia (significantly impaired speech func-tion with relative sparing of the written language) is a common phenomenon and patients tend to function with writing, typing and other electronic language devices in the initial stages[6,16]. The neuroanatomical correlate of nfvPPA is considered to be Broca's area (Broadman area 44/45)[15]. Apraxia of speech (difficulty produce normal phonation and prosody of speech) was originally described in nfvPPA[16]. However, studies on apraxia of speech are now shedding light on new understanding that initial predominant apraxia of speech is entirely a different entity called Primary Progressive Apraxia of Speech[22,23] while some are believing it is still a subtype of nfvPPA.

Frontotemporal Dementias Related Syndromes

Frontotemporal Dementia with Motor Neurone Disease

The association was noted first after the world war II, in the Guamanian Chamorros as "guam complex" (atypical parkinsonism, MND and FTD). Despite extensive international research, the cause of this association is still unclear and reduced prevalence of guam complex made it to assume that it is an environmental cause rather than genetic[24].

However current FTD-MND syndrome is characterised by coexisting criteria fullfilling FTD and Motor Neurone Disease (MND). FTD-MND patients are having lesser life expectancy than average FTDs. The association is much common with bvFTD than PPAs. The association is now more characterised after the establishment of its histopathological and genetic overlap. There are several genes described such as FUS, TDP-43, CHCHD10, UBQLN2, TBK1, VCP, SQSTM1 and most importantly C9orf72 associated with FTD-MND[25].

Corticobasal Degeneration

Corticobasal degeneration (CBD) was first described on autopsy studies in 1968, by Rebeiz. "Corticodentatonigral degeneration with neuronal achromasia" was the original description of the CBD pathology[26]. Corticobasal Syndrome (CBS) is used to describe the classic clinical syndrome associated with the CBD pathology. There are CBS cases not associated with CBD pathology and vice versa[6]. To diagnose probable CBS, patient should present with asymmetric presentation with two of the following motor symptoms (limb rigidity or akinesia, limb myoclonus, limb dystonia) and two of the following higher cortical functions (limb or orobuccal apraxia, cortical sensory impairment and alien limb phenomenon)[27]. Interestingly CBD is more likely to be symmetric than CBS, while asymmetric cases also do exist. CBD patients typically presents with initial behavioural, language or dysexecutive syndrome that may suggest bvFTD or nfvPPA and later develop motor symptoms such as parkinsonism with axial rigidity[28]. There are no specific biomarkers that predict CBD pathology to date.

Progressive Supranuclear Palsy

Progressive Supranuclear Palsy syndrome (PSP-S) was first described in 1964 by Steele, Richardson and Olszewski and known as the eponymous syndrome of the authors (Steele Richardson Olszewski Syndrome)[30]. There are several sub types of PSP has been described. Williamson in 2009, proposed the most widely used classification. He classified the classic Richardson syndrome as PSP-S. PSP-Parkinsonism (PSP-P) is the most common non-Richardson subtype which differentiate from PSP-S by having tremor and mild levodopa respon-

siveness. PSP-pure akinesia with gait freezing (PSP-PAGF) is a slowly progressive disease despite of severe atrophy in the globus pallidus, substantia nigra and subthalamic nuclei. In addition, PSP-Corticobasal Syndrome (PSP-CBS) and PSP-progressive nonfluent aphasia (PSP-PNFA) have been described[31].

While majority of patients with PSP-S presents with classic PSP syndrome, a minority with bvFTD or nfvPPA can later develop PSP-S or Initial presentation of PSP may eventually progressed to bvFTD or nfvPPA[32,33].

Neuropathology of FTDs

"Frontotemporal lobar degeneration" (FTLD) is a selective neurodegenerative process that results in neuronal loss and gliosis of the frontal and temporal lobes of the brain[34]. The term FTLD also loosely used to group the diverse array of pathological substrates that is associated with FTDs. Some of these pathologies are described with neurodegenerative processes other than the spectrum of FTDs as well.

FTLD-tau is discovered in 1975. In Pick's disease, pick bodies are mainly composed of 3 repeat tau (3R tau). 4 repeat tau (4R tau) is predominantly described in CBS, PSP, globular glial tauopathy (GGT) and argyrophilic grain disease (AGD)[6]. The latter two are rare FTDs and a detailed discussion is not intended in this review (see Figure 1).

TAR DNA- binding protein 43 (TDP-43) is the main neuropathology of FTLD-U (tau negative and Ubiquitin positive) and amyotrophic lateral sclerosis (ALS). There are 4 TDP-43 sub types (TDP-43 Type A, B, C and D). FUS (Fused in Sarcoma) is linked to FET protein family. FET consists of FUS and other RNA/DNA binding proteins of Ewing's sarcoma (EWS) and TATA-binding protein-associated factor 15 (TAF15)[6]. Neuronal intermediate filament inclusion disease (NIFID), Basophilic inclusion body disease (BIBD) are rarely encountered FTLD pathologies.

This diagram summarizes the overlap of FTD spectrum disorders with neuropathology.

A small portion of clinical syndromes being caused by AD pathology. lvPPA is highly correlated with AD pathology.

FTLD-tau
3R (3 repeat tau),
4R (4 repeat tau),
FTLD-TDP(TAR DNA-binding protein 43)
FTLD-FET(fused in sarcoma, Ewing's sarcoma, TATA-binding protein-associated factor 15)
FTLD-UPS(ubiquitin-proteasome system)
aFTLD-U (atypical FTLD with ubiquitin inclusions
NIFID (Neuronal intermediate filament inclusion disease)
BIBD (Basophilic inclusion body disease)

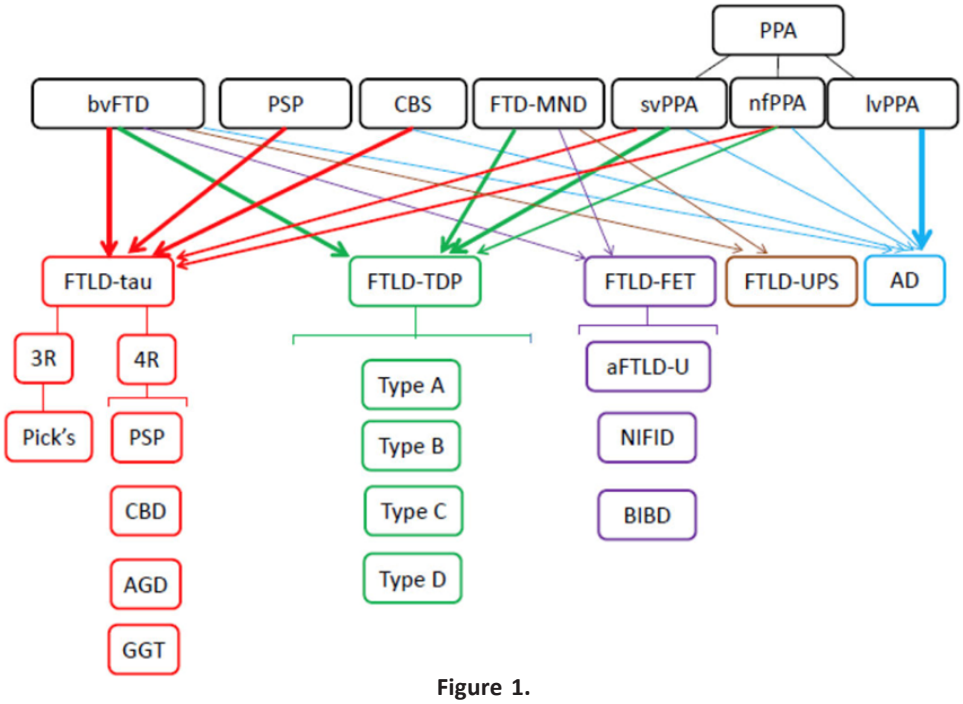

Figure 1.

(Reprinted from *Neurology Clinics* 2017; **35**(2): 339-374, Olney NT, Spina S, Miller BL. Frontotemporal Dementia, with permission from Elsevier.

FTD Genetics

Although majority of FTDs are sporadic, up to 40% can have a family history of dementia, psychiatric disorder or motor symptoms. At least 10% can have autosomal dominant pattern[35]. Genetics are mostly described in FTD-MND which is the most heritable category while svPPA is the group which is least heritable[36].

C9orf72, MAPT and GRN are the three most common genes associated with FTDs. There are several less common genes such as VCP, CHMP2B, TARDBP, FUS, EXT2, TBK1 and SQSTM1 that are associated with FTDs.

Treatment of FTDs

To date there are no FDA approved treatment for FTDs. However, clinicians who are managing patients with FTD, use off-label medication and behavioural therapy. Alzheimer disease treatment has not demonstrated to be useful in FTDs. Sometimes acetylcholine esterase inhibitors may aggravate FTD symptoms.

Off label use of selective serotonin uptake inhibitors (SSRIs) are acceptable for behavioural symptoms[38]. Behavioural symptoms of FTD could also be treated with atypical antipsychotics, but one should be cautious about the potential extrapyramidal side effects.

Nonpharmacological therapies are helpful when there's no specific pharmacological treatment available. Caregiver education and training about behavioural, environmental and physical techniques to redirect unwanted behaviours has been utilized in FTDs[39]. Physical exercise has been demonstrated to delay cognitive decline and should consider in all patients whenever it is safely administrable[40]. Primary progressive aphasia patients may benefit from regular speech and language therapy programme.

Although there is no FDA approved treatment, the expanding knowledge on pathology and neurogenetics has given hope for the researchers for development of several therapeutic targets and several clinical trials are currently underway. A molecular based FTD therapeutic is not hopefully far away.

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Point of view

Cerebral microbleeds and stroke: more questions than answers

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Abstract

With the widespread availability of MRI scanning, cerebral microbleeds (CMBs) are being increasingly recognised in patients with stroke and in healthy individuals. As CMBs are commonly viewed as markers of increased risk of intracerebral haemorrhage (ICH), there are concerns regarding the use of antithrombotic agents (antiplatelets, and especially anticoagulants) in the presence of CMBs, even in patients at high risk of ischaemic events. The use of antiplatelet or anticoagulant therapy in the presence of CMBs, balancing the risk of recurrent ischaemic stroke against the risk of possible intracranial bleeding, is one of the most contentious contemporary issues in stroke medicine.

Key words: cerebral microbleeds; stroke; intracerebral haemorrhage; ischaemic stroke; antiplatelets; anticoagulants

What are cerebral microbleeds?

CMBs are a radiological biomarker of cerebral small vessel disease. They are seen on blood-sensitive MRI sequences such as T2*-weighted gradient-recalled echo (T2*-GRE) or susceptibility-weighted imaging (SWI)[1,2,3,4,5,6]. They are small (usually <5 mm in diameter), rounded or oval lesions of low signal intensity in the brain parenchyma[1,2,3,4,7,8]. CMBs represent haemosiderin deposits contained within macrophages in the microvascular perivascular spaces on histopathological examinations[1,2,3,4,9], and develop as a result of leakage of red blood cells secondary to rupture of the walls of small arteries, arterioles or capillaries[1,2,10]. Whether the rupture of a small vessel results in a microbleed or a larger macrobleed is believed to depend on different vasculopathic features and environmental exposure[5,7]. Two distinct patterns of microangiopathy are noted on histopathological testing in the blood vessels located near CMBs: lipohyalinosis and cerebral amyloid angiopathy (CAA). The pattern of microangiopathy appears to determine the pattern of anatomical distribution of CMBs; lobar CMBs are associated with CAA in superficial perforating arteries, deep subcortical or infratentorial CMBs result from arteriosclerosis or lipohyalinosis related to hypertensive arteriopathy of deep perforating arteries, and a mixed distribution in both locations is seen with a mixed pattern of microangiopathy[2,3,5,6,9,11].

CMBs: What do they mean?

Prevalence of CMBs is highly variable, depending on the demographic and clinical characteristics of the population studied and the MRI criteria of assessment. They are reported in 3-27% of the general population, and 6-80% of patients with vascular risk factors or vascular disease[2]. In population studies, CMBs were associated with older age, hypertension, diabetes, smoking and previous stroke[2,3,6,12].

CMBs and stroke

CMBs are more prevalent in patients with stroke, and in patients with ICH than ischaemic stroke[1,2]. In a systematic review, CMBs were seen in 5% of healthy adults compared to 45% of patients with any stroke, 34% with ischaemic stroke and 60% with ICH[12].

CMBs predict increased stroke risk. In a meta-analysis, CMBs increased the risk of ischaemic stroke (odds ratio [OR]: 2.14), ICH (OR 4.65) and death (hazard ratio: 1.36)[13]. CMBs are a marker of small vessel disease. They are more frequent in patients with lacunar strokes than cortical strokes[1,2,14,15,16], and in those with a higher burden of white matter lesions (WMLs) in periventricular or deep white matter regions[1,12,14]. CMBs are reported to be twice as frequent in patients with lacunar strokes (26%) than cortical strokes (13%)[1].

CMBs are commoner among patients with recurrent strokes than first-ever strokes[12,17]. In pooled data from 54 studies, CMBs were seen in 23% with first-ever ischaemic stroke and 52% with first-ever ICH, compared to 44% with recurrent ischaemic stroke and 83% with recurrent ICH[12]. The risk of stroke recurrence appears to be greater with lobar CMBs[11,13,14], and in the presence of ≥5 CMBs[2,16,18].

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In patients with atrial fibrillation (AF), CMBs are more prevalent[19,20,21], and are associated with ischaemic stroke[19,20] and asymptomatic cerebral infarction[21]. They are reported in 30-56% of patients with AF and ischaemic stroke[7,19,20,22]. Prior antiplatelet therapy is independently associated with the presence of CMBs in patients with AF[20]. CMBs are also related to prior anticoagulation with warfarin in patients with AF, but not with non-vitamin K antagonist oral anticoagulants (NOACs)[8].

CMBs and intracerebral haemorrhage

CMBs increase the risk of ICH, particularly in patients with multiple lobar CMBs (which indicates probable underlying CAA). In a meta-analysis of data from 10 studies involving ICH survivors, a consistent association between CMB presence at baseline and risk of future ICH recurrence was seen. The risk of recurrent ICH varied with the distribution and burden of CMBs, and the underlying microangiopathy[7]. In presumed CAA-related ICH (based on a lobar distribution of ICH), the risk of recurrent ICH was 7-fold higher compared to CAA-unrelated ICH; the risk was higher in those with CMBs (28.7%) compared to those without (11.3%), and in those with a higher CMB burden. Even in CAA-unrelated ICH, the risk of recurrent ICH was higher in those with CMBs (4.6%) compared to those without (1.2%), but only the presence of more than 10 CMBs was associated with an increased risk. The presence of a single CMB did not increase the risk of recurrent ICH[7].

CMBs and ischaemic stroke

In patients with ischaemic stroke, CMBs increase the risk of both ischaemic and haemorrhagic stroke recurrence. In a meta-analysis of ten prospective cohorts with ischaemic stroke or TIA, the presence of CMBs was associated with an increased risk of recurrent stroke (OR 2.25), and the risk was greater for recurrent ICH (OR 8.52) than for recurrent ischaemic stroke (OR 1.55)[11]. Pooled analysis of individual patient data from 38 cohort studies in the Microbleeds International Collaborative Network showed that in patients with previous ischaemic stroke or TIA, the presence of CMBs on baseline neuroimaging was associated with increased risk of both ischaemic stroke and ICH, and the risk of ICH was higher than that of ischaemic stroke. The adjusted hazard ratio (comparing patients with CMBs vs. no CMBs) was 1.35 for any stroke, 2.45 for ICH and 1.23 for ischaemic stroke. The CMB burden correlated with the comparative risks of ICH and ischaemic stroke, with the risk of ICH 5 times higher than the risk of ischaemic stroke in the presence of ≥10 CMBs, and 8 times higher with ≥20 CMBs[10]. However, the absolute rate of ischaemic stroke consistently exceeded that of ICH, irrespective of age, CMB anatomical distribution, CMB burden, antithrombotic treatment and a diagnosis of probable cerebral amyloid angiopathy[10]. Similarly, the presence of CMBs was associated with a higher risk of developing new ischaemic strokes than of ICH in a European cohort of patients with ischaemic stroke or TIA[14].

CMBs and antithrombotic therapy

Antiplatelet treatment, and to a greater extent anticoagulant treatment, increase the risk of ICH in patients with CMBs[2]. In two large prospective cohorts, patients with a high CMB burden and on antiplatelet therapy following ischaemic stroke or TIA had increased risk of both ischaemic and haemorrhagic stroke [16]. In a prospective observational study of patients on anticoagulation therapy for AF with ischaemic stroke or TIA (CROMIS-2), the presence of CMBs at baseline was independently associated with increased risk for symptomatic ICH (sICH rate - 9·8 per 1000 patient-years with CMBs compared to 2.6 without CMBs)[22]. In the NAVIGATE-ESUS trial, use of rivaroxaban in patients with cryptogenic stroke was associated with a 4-fold increase in the risk of ICH, and the risk was greater with a higher CMB burden[23]. Some studies have reported higher rates of ICH, disability and mortality in patients with >10 CMBs when treated with intravenous thrombolysis for ischaemic stroke, especially in older age and with longer treatment delays[24]. However, others have not found similar increased bleeding risks with thrombolysis[25].

CMBs – To treat or not to treat?

Patients with recent ischaemic stroke or TIA are at risk of recurrent ischaemic events, but the risk of ICH with antithrombotic therapy is greater in the presence of CMBs. This has led to a therapeutic conundrum in patients with a history of stroke and CMBs detected on MRI, with concerns expressed regarding the use of antithrombotic treatment, especially anticoagulants[2,16,23]. It has been suggested that patients with lobar ICHs and numerous lobar CMBs, with the possibility of underlying CAA and associated high risk of rebleeding, should not receive anticoagulants[2].

However, there is increasing evidence that CMBs are not only markers of a haemorrhage-prone arteriopathy but also markers of recurrent ischaemic events[12]. Recent data has shown that the absolute risk of recurrent ischaemic stroke is higher than the risk of ICH in patients with ischaemic stroke or TIA and CMBs, even with a high CMB burden[10,22,23,26]. In a pooled analysis of data from 38 cohort studies in the Microbleeds International Collaborative Network, the rate of recurrent ischaemic stroke was 64/1000 person-years, compared to symptomatic ICH rate of 27/1000 person-years, in the presence of ≥10 CMBs[10]. In the CROMIS-2 study of patients on anticoagulation therapy for AF following ischaemic stroke or TIA, the absolute event rate of

ischaemic stroke in patients with CMBs (24.1 per 1000 patient-years) was much higher than the absolute event rate of symptomatic ICH (9.8 per 1000 patient-years)[22]. A recent study of patients with acute ischaemic stroke and AF treated with oral anticoagulants has yielded similar results. The presence and burden of CMBs were associated with an increase in vascular events (ICH, ischaemic stroke or vascular death) on long term follow up, and the absolute rates of ischaemic stroke were higher than those of ICH at all levels of CMB burden[26]. In a subgroup analysis of the NAVIGATE-ESUS trial, the presence of CMBs did not influence the risk of ICH in patients with cryptogenic stroke treated with rivaroxaban[23]. Further, no interaction was noted between single or dual antiplatelet therapy and the presence of CMBs for the outcomes of recurrent ischaemic or haemorrhagic stroke in patients with lacunar infarcts in the SPS3 trial[7]. More recent data demonstrate that starting antiplatelet treatment may not be associated with an increased risk of bleeding in the presence of CMBs even in patients with ICH. In the RESTART trial, CMB presence, burden or location was not associated with a higher risk of recurrent ICH in patients treated with antiplatelet therapy following an ICH[27].

These data suggest that the CMB presence, pattern or burden should not influence the decision to select appropriate antithrombotic therapy for secondary stroke prevention. Withholding antithrombotic treatment based on the presence of CMBs is not supported by current evidence[10,12,23,26,28].

CMBs – more uncertainties

Management of patients with CMBs poses several more therapeutic dilemmas. Several factors such as blood pressure variability and control and concurrent antithrombotic drug use can increase ICH risk, in addition to the presence of CMBs. There is no data regarding their relative contribution to ICH risk[7]. The ongoing APACHE-AF trial is expected to provide more insights into the use of NOACs in patients with AF and a recent ICH[29].

There is a well-known geographical variation in ICH risk, with ICH being commoner in Asian, especially Far Eastern, populations. Their vascular risk factor profile is different, with a higher prevalence of hypertensive arteriopathy. Asians also have a higher CMB prevalence compared to Western populations, in both ischaemic stroke and ICH patient groups[12,16,23]. Their CMB distribution is different, with higher rates of non-lobar (deep or infratentorial) CMBs, and hypertensive arteriopathy rather than CAA is believed to contribute to the elevated ICH risk in Asians[30]. The balance of risk for developing ICH compared to ischaemic stroke in the presence of CMBs appears to be different between Asian and Western populations, with Asians with CMBs more likely to develop ICH and Western populations more likely to develop ischaemic stroke[11]. Further studies are needed to better understand the complex effects of ethnicity and genetics on CMB prevalence and associated ICH risk.

Of particular interest are the intriguing results of a recent study which identified *Streptococcus mutans*, an oral pathogen responsible for dental caries, in a large number of stroke patients with CMBs, suggesting a possible association between the oral microbiome and cerebral microbleeds[31]. It has been postulated that *S. mutans e*xpressing the cnm gene can enter the blood stream from the oral cavity, attach to the cerebral vasculature, disrupt the blood-brain barrier, and lead to the development of CMBs[31]. This raises the exciting possibility of treating CMBs with antibiotics to reduce stroke risk.

Key learning points

- Cerebral microbleeds (CMBs) are a radiological biomarker of cerebral microangiopathy.
- Lobar CMBs are associated with cerebral amyloid angiopathy in superficial perforating arteries, and subcortical CMBs with hypertensive arteriopathy in deep perforating arteries.
- CMBs are more prevalent in patients with both haemorrhagic stroke and ischaemic stroke, and are a marker for small vessel disease.
- In patients with intracerebral haemorrhage (ICH), CMBs increase risk of recurrent ICH, and in patients with ischaemic stroke, CMBs increase risk of recurrent stroke, both ischaemic and haemorrhagic.
- The absolute event rate is higher for ischaemic stroke than for ICH in patients with stroke and CMBs.
- There is no evidence to support a policy of withholding antithrombotic treatment in patients with stroke and CMBs.

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Case report

Intracerebral haemorrhage due to vaccine-induced immune thrombocytopenia and thrombosis

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Key words: vaccination, thrombosis, thrombocytopaenia, intracerebral haemorrhage

Introduction

Vaccine-induced Immune thrombocytopenia and thrombosis (VITT) is a rare complication following vaccination with the ChAdOx1 nCov-19 [recombinant adenoviral vector encoding the spike protein antigen of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)]. VITT has been reported in several countries and there are no published reports of this entity from Sri Lanka[1]. We report a case of VITT causing fatal intra-cerebral haemorrhage (ICH) following ChAdOx1 nCov-19 vaccination.

Case report

A 61-year-old housewife with a history of type 2 diabetes mellitus and dyslipidaemia presented with right face, arm and leg weakness and slurred speech on waking up from bed. She was last known to be well 6 hours ago. She was administered SARS-CoV-2 adenoviral vector vaccine two weeks ago after which she developed mild fever and headache which resolved in four days.

On examination she was conscious and rational, pulse 88 per minute and regular, blood pressure 160/95 and had right hemiparesis and dysarthria. Non-contrast CT brain done on admission was normal (Figure 1). She was not thrombolysed as the time of onset of stroke was uncertain. Antiplatelets and statin therapy was initiated.

Twelve hours following the admission she developed generalized tonic-clonic seizures and the Glasgow coma scale (GCS) dropped to 8/15. Non contrast CT brain was repeated following seizures and revealed left intra-cerebral and intraventricular haemorrhage (Figure 2). Laboratory investigations are summarized in Table 1.

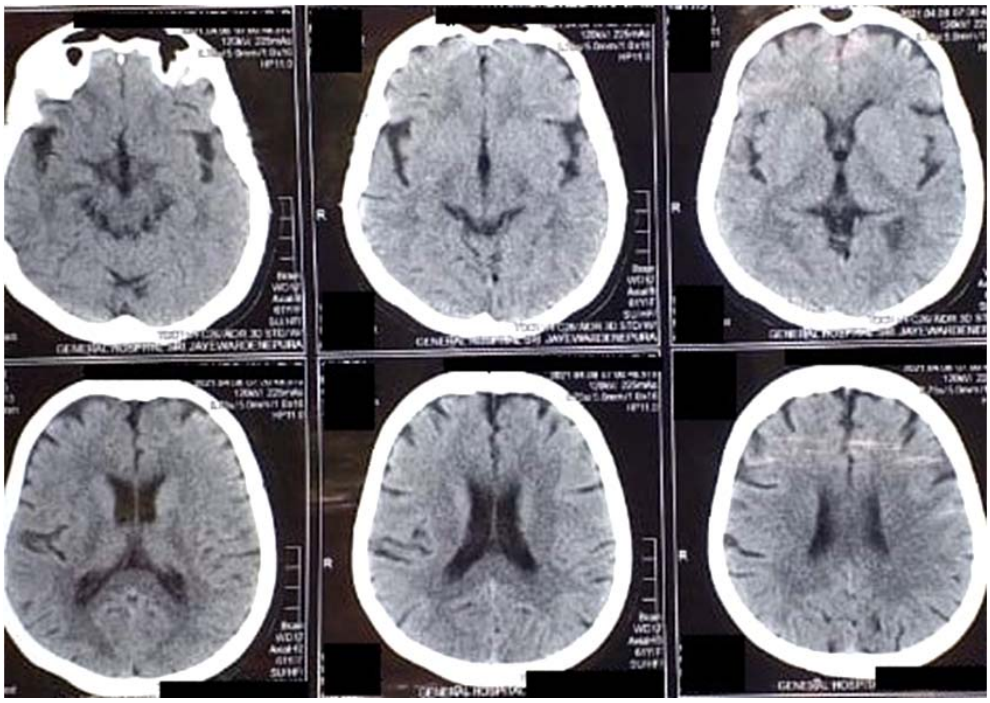

Figure 1. Normal non-contrast CT of brain on admission.

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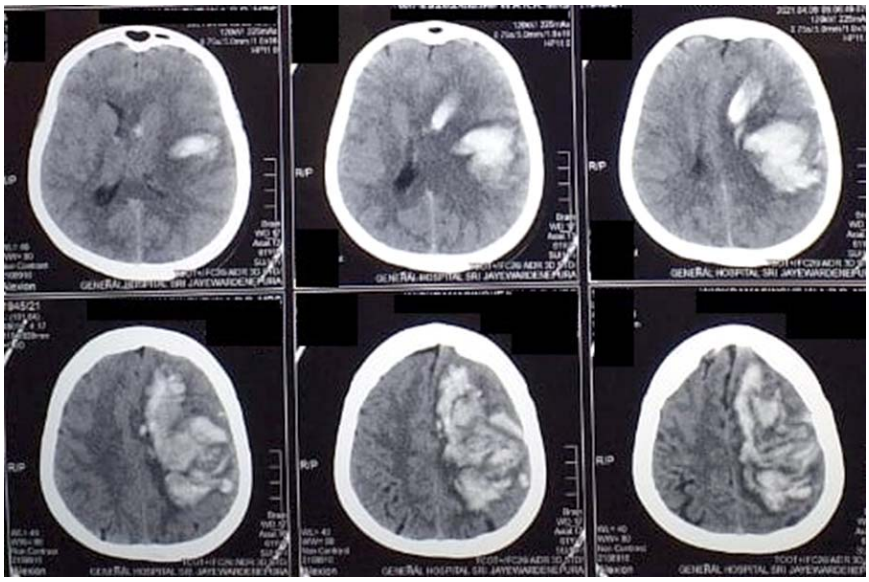

Figure 2. Non-contrast CT of brain at 12 hours after admission showing large intra-cerebral and intraventricular haemorrhage on the left side.

Table 1. Summary of laboratory investigations on day 1 and day 2 after admission

Laboratory Analysis	*Reference value*	*Day 1*	*Day 2*
Haemoglobin (g/dl)	11.0-16.0	13.4	7.7
Platelet count (10^3/ul)	150-400	55	27
Leucocytes (10^3/ul)	4.00-11.00	10.2	15.4
APTT(s)	22-36	26	39.9
PT(s)	12-15	11.5	17.3
TT(s)	15-21	18.8	26.5
D-Dimer (ng/ml)	<550	>10,000	N/A
Creatinine (umol/l)	51-106	72	93
CRP (mg/dl)	<6	18	26
Dengue Antigen		Negative	N/A
Dengue Antibodies		IgM negative	
IgG positive	N/A		

Antiplatelet therapy was withheld and urgent neurosurgical referral was done. She was transferred to neurosurgical intensive care unit where she was intubated and ventilated. Craniotomy was not performed due to severe coagulopathy. An external ventricular drain was placed after correction of coagulopathy with cryoprecipitate and fresh frozen plasma. It was planned to initiate intravenous immunoglobulin. However, her GCS dropped to 3/15 with haemodynamic instability and died on 2nd day of admission.

Table 2. Diagnostic criteria for VITT (2)

Type of VITT	*Description*
Definite VITT	All five of the following criteria. 1. Onset of symptoms 5-30 days after vaccination against SARS-CoV-2 2. Presence of thrombosis 3. Thrombocytopaenia (platelet count <150,000/mm^3) 4. D-dimer level >4000 FEU 5. Positive anti-PF4 antibodies on ELISA
Probable VITT	D-dimer level > 4000 FEU but one criterion not met (timing, thrombosis, thrombocytopaenia or anti-PF4 antibodies)
Possible VITT	D-dimer level unknown or 2000-4000 FEU with one other criterion not met or two criteria not met.

(FEU = Fibrinogen equivalent units)

Discussion

VITT is an immune thrombocytopaenia and thrombosis mediated by platelet activating antibodies against platelet factor – 4 (PF-4) and presents 5-30 days after vaccination[2]. Diagnostic criteria of VITT are given in table 2. This patient fulfilled the diagnostic criteria for probable VITT. VITT commonly causes intracranial or extracranial venous thrombosis. In one of the largest case series studied, 42 out of 220 patients had intracranial haemorrhage secondary to venous thrombosis[2]. Intracerebral haemorrhage in this patient was most likely secondary to cerebral vein thrombosis (resulting in 18-fold rise in d-dimer level) coupled with severe thrombocytopaenia. Antiplatelet therapy at admission would have contributed.

Treatment of VITT remains uncertain. Use of IV Immunoglobulin 1g/kg for 2 days has been used to raise the platelet count and reduce hypercoagulability (2-4). Heparin-based anticoagulants and warfarin should be avoided. Direct oral Xa inhibitors, and direct thrombin inhibitors can be used in the absence of bleeding. Platelet transfusions should be avoided except in the presence of major bleeding. The mortality is higher among patients with a platelet count of <30,000 per cubic millimeter, cerebral venous sinus thrombosis and intracranial haemorrhage. Plasma exchange can be used in patients with platelet count of <30,000 per cubic millimeter and intracranial haemorrhage. Overall case-fatality rate was 22% which increases to 73% in patients with a platelet count less than 30,000/mm^3 and intracranial haemorrhage.

Key Points

- VITT is a rare but a serious complication of ChAdOx1 nCov-19 vaccination.
- VITT is an immune thrombocytopaenia and thrombosis mediated by anti-PF-4 antibodies.
- VITT should be suspected in any patient with symptoms of a stroke presenting 5-30 days after vaccination for COVID-19.
- Antiplatelet drugs, warfarin and heparin-based anticoagulants should be avoided if VITT is suspected and until a diagnosis of VITT is safely excluded.
- Treatment of VITT remains uncertain.

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Case report

COVID-19 associated unilateral sciatic neuropathy

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Sri Lanka Journal of Neurology, 2021, **8**, 18-19

Abstract

A 36-year-old woman developed right leg weakness with foot drop while being treated for COVID-19 pneumonia. Her nerve conduction test and electromyography confirmed right sciatic nerve lesion and MRI scan of the lumbar spine, sciatic nerve, and examination of cerebrospinal fluid were unremarkable. Since there was no other possible explanation, the cause was attributed to a neurological complication of COVID-19 infection.

Introduction

In the latter part of 2019, Corona Virus Disease 2019 (COVID-19) epidemic emerged and spread rapidly across the globe becoming a pandemic by March 2020. The causative virus is known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The most common manifestation of the disease is respiratory system related symptoms. Although the neurological manifestations are not the commonest, the scale of the current pandemic could result in large number of cases with neurological complications[1].

The neurological manifestations could be para-infectious or post infectious. The reported neurological manifestations of the disease include anosmia, meningitis, encephalitis, myelitis, central nervous system (CNS) vasculitis, acute disseminated encephalomyelitis (ADEM), Bell's Palsy, Guillain-Barré syndrome (GBS), other acute neuropathies and stroke. These manifestations may be related to non-specific complications of the systemic disease, direct invasion by the virus or the inflammation of the nervous system or the vasculature[2,6].

In this case report we present a case of COVID-19-related unilateral sciatic mono-neuropathy.

History

A 36-year-old woman with no previous co-morbidities, who was unvaccinated for COVID-19, presented with fever and shortness of breath. She had a positive SARS-CoV-2 polymerase chain reaction (PCR) test on nasopharyngeal swab on 13th of June 2021. With the worsening of respiratory symptoms, she was diagnosed as COVID-19 pneumonia and admitted to the High Dependence Unit. She received oxygen therapy, subcutaneous enoxaparin, and dexamethasone, empirical antibiotics, but no biologics for her pneumonia. On 25th of June 2021 (after 12 days from presentation) during her HDU stay, she developed weakness of right leg with foot drop and paraesthesia.

The neurological examination revealed, a high stepping gait due to right foot drop, weakness in knee flexion (MRC 3/5), ankle plantar flexion (MRC 2/5) and ankle dorsiflexion (MRC 2/5). Normal power was observed in hip flexion, extension, abduction, and adduction as well as knee extension.

The right ankle reflex was absent with preserved knee reflex. Sensory impairment was noted below knee except for a narrow area down the medial side of the lower leg and along the medial boarder of the foot. Examination of left lower limb and both upper limbs were neurologically normal. She did not have cranial nerve impairment.

The electromyogram showed, severe proximal right sciatic nerve neuropathy with preferential involvement of the peroneal fibres. MRI lumbosacral spine showed normal vertebral heights, disc spaces and roots. The MRI scan of right sciatic nerve showed normal signal intensity and anatomy, and no contrast enhancement was seen. Cerebrospinal fluid (CSF) analysis showed normal protein, cells, and sugar. CSF was negative for PCR and antibodies for SARS-CoV-2 while her serum showed positive SARS-CoV-2 antibody response. Her inflammatory markers were high during the acute phase of her pneumonia, but antinuclear antibodies (ANA), anti-neutrophil cytoplasmic antibodies (ANCA) were negative.

Discussion

Although SARS-COV-2 has main manifestations related to the respiratory system, neurologic complications are not uncommon. A recent study found 36.4% of patients with COVID-19 develop neurological symptoms. Anosmia, myalgia, headache, encephalopathy, and dizziness are most common neurological manifestations. Severely affected patients are more likely to develop neurological symptoms than patients who have mild or moderate disease[3].

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The exact mechanisms of nervous system involvement by the SARS-CoV2 virus are still unknown. However, the possible routes of transmission could be retrograde neuronal transport across infected neurons, entry via the olfactory nerve, infection of the vascular endothelium, leucocytes migration across the blood-brain barrier, or via angiotensin-converting enzyme-2 receptors found on neurons and glial cells[8].

Peripheral nerve involvement in COVID-19 is not commonly reported and the available literature is limited. The mechanism of peripheral nerve involvement is not well understood and probably a result of inflammatory or immunological response of neurons to the virus.

Guillain-Barré syndrome (GBS) or its variants are one of the common manifestations of peripheral neuropathy related to SARS-CoV-2. These neurological manifestations began at a median of 7 days (7 to 24) after respiratory or systemic features. A review on neurological complications of COVID-19 stated, out of 12 GBS patient's 8 had demyelinating disease and axonal disease in remainder[2].

A case of peripheral neuropathy with electrophysiological evidence of mixed sensorimotor neuropathy had been reported. There is a case of painful neuropathy associated with the COVID-19, which is an uncommon type of a neuropathy[4]. A case of sciatic neuropathy was reported by Acharya et al with some similarities to the case we have reported[5].

In our case of right leg weakness following COVID-19 infection, the neurophysiological studies confirmed a right sided severe proximal sciatic nerve lesion. The MRI of the lumbosacral spine was normal with no enhancement to indicate radiculitis. Her CSF protein and cells were normal and SARS-COV-2 antibodies were negative.

The normal imaging has excluded a structural cause for the nerve lesion. The normal CSF makes an inflammatory radiculopathy less likely. Absence of CSF SARS-COV-2 antibodies makes an intrathecal production of immunoglobin G or disruption to the blood brain barrier less likely. She was not intubated, and her consciousness was intact throughout the hospital stay which makes a neuropraxic sciatic nerve lesion due to compression improbable. Unilateral involvement negates the possibility of critical illness neuropathy. Involvement of the sensory findings exclude the possibility of the anterior horn cell lesion.

Our patient was managed with oral dexamethasone short course, physiotherapy and rehabilitation with ankle foot orthosis and made a moderate improvement.

It is possible that the nerve involvement may be immune mediated or a direct viral effect on the peripheral nerve. We did not consider a nerve biopsy since the neurological deficits as a complication could be devastating and the patient made a moderate improvement with treatment.

Conclusion

Although neurological manifestations are now being reported in relation to COVID-19, mono-neuropathies are rare. It is important to consider COVID-19 as a differential diagnosis for the large nerve neuropathies in the appropriate context. Studies of more cases are necessary to define this entity, pathophysiology, and therapeutics since they can result in long term disability.

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Case report

Persistent hiccups as a rare presentation of Ramsey Hunt syndrome in a renal transplant recipient

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Key words: multiple cranial nerve palsy, hiccups, Ramsey Hunt syndrome, Varicella zoster virus, renal transplant recipient

Ramsay Hunt syndrome type 2, also known as RHS and herpes zoster oticus, is a disorder that is caused by the reactivation of varicella zoster virus in the geniculate ganglion, a nerve cell bundle of the facial nerve. RHS typically presents with inability to move many facial muscles, pain in the ear, taste loss on the front of the tongue, dry eyes and mouth, and a vesicular rash. However, the association of RHS with multiple cranial nerve involvement and persistent hiccups is less well reported.

Patient information

A 29-year-old male presented with right ear pain, tinnitus and sore throat followed by fever, unbearable hiccups, vomiting and difficulty swallowing over four days. He had undergone a related live donor renal transplant 15 years back and was on mycophenolate mofetil.

The patient was conscious and rational. There were erythematous vesicles in the right external ear (Figure 1) and the soft palate (Figure 2). Neurological examination revealed lower motor neuron type facial nerve palsy (Figure 3), sensory-neural type hearing loss, and palatal palsy with impaired palatal sensation on the right side. Hoarseness of voice and nasal regurgitation of liquids while swallowing was noted. Stroboscopy confirmed right-sided vocal cord palsy (Figure 4). He had horizontal nystagmus on the left side and a positive right head impulse test. The rest of the cranial nerves and optic fundal examination were normal. He did not have neck stiffness. Upper limb, lower limb, and cerebellar examination were normal. His blood pressure, pulse rate and respiratory rate were normal.

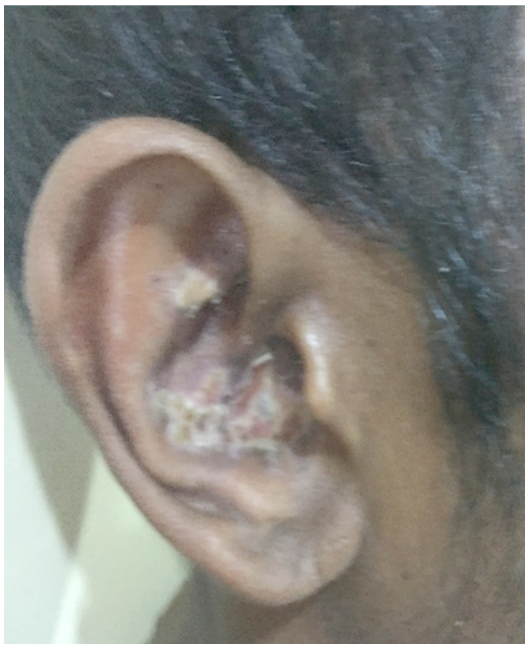

Figure 1. Vesicles in the right external ear.

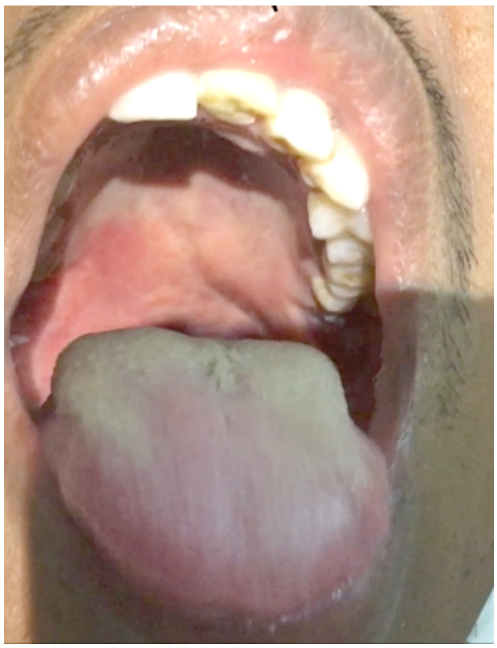

Figure 2. Right-sided palatal palsy and redness of the soft pallet.

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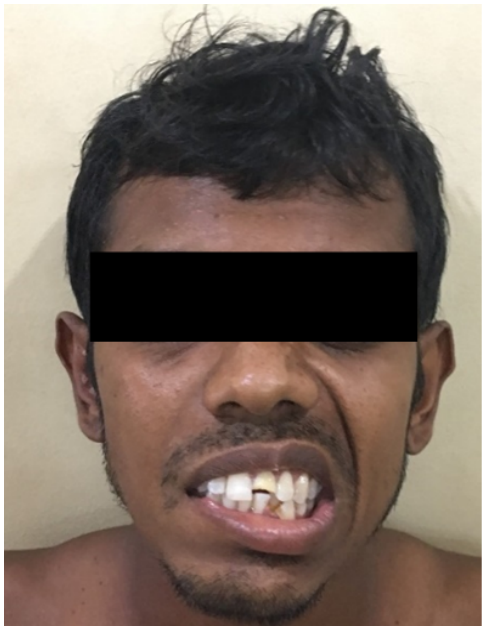

Figure 3. Right facial nerve palsy.

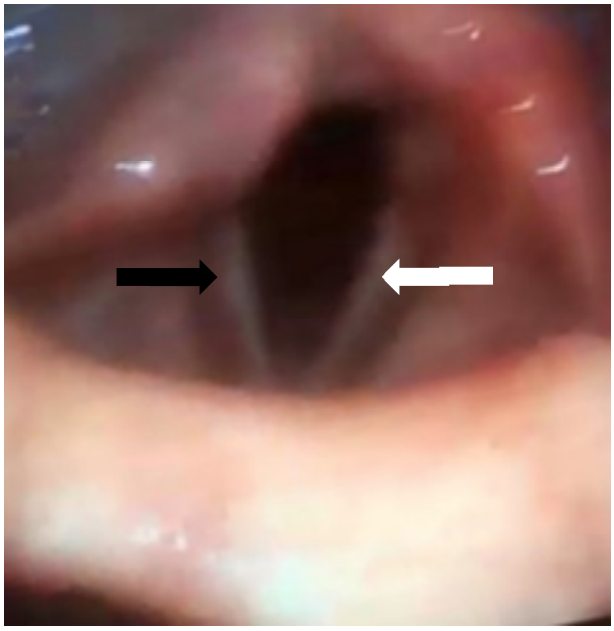

Figure 4. Stroboscopy view of normal left vocal cord (white arrow) and right vocal cord palsy (black arrow).

Diagnostic assessment

The full blood count revealed neutrophil leucocytosis. C-Reactive Protein (CRP) was 45 mg/dl. His baseline serum creatinine of 256 micromole/L increased to 270 micromol/L and remained stable. Serum electrolytes, calcium and transaminases were normal. The non-contrast MRI brain was normal.

Cerebrospinal fluid (CSF) analysis revealed an opening pressure of 12 cmH_2O, 40 lymphocytes, 40 mg/dl protein, and 76mg/dl sugar (random blood glucose was 113 mg/dl). CSF, right ear vesicle fluid, urine and blood bacterial cultures were sterile. CSF for myco-bacterium tuberculosis, cytomegalovirus, herpes simplex virus, cryptococcal antigen and Toxoplasma IgM antibodies were negative. The stool for Enterovirus and Adenoviral panel was negative. HIV-1/HIV-2 antibodies and VDRL were negative. Diaphragmatic ultrasound scan and chest X-ray were normal. Blister swab from the ear canal and the CSF was positive for Varicella Zoster Virus (VZV) DNA. Ramsay Hunt syndrome (RHS) involving multiple (VII, VIII, IX, X) cranial nerves was diagnosed.

He required a nasogastric tube to prevent aspiration, optimize nutrition and provide oral medications. He was started on a renal adjusted dose of intra-venous acyclovir along with an empirical broad-spectrum antibiotic (ceftriaxone and teicoplanin). Persistent hiccups were extremely troublesome and required symptomatic treatment with domperidone and metoclopramide for several days. He was treated with prochlorperazine for five days and betahistine for three months with regular vestibular rehabilitation physiotherapy. After confirming the right-sided partial sensory-neural hearing loss by an audiogram, intratympanic dexamethasone therapy was commenced. Empirical antibiotics were discontinued after negative culture reports. Intravenous acyclovir was continued for 21 days. Post-treatment CSF was negative for VZV DNA.

Follow-up and outcomes

The patient was discharged after the completion of the antiviral treatment. On discharge hiccups, ear and throat vesicles had resolved. Nasogastric tube feeding was continued for three months. Six cycles of intratympanic dexamethasone injections were given over three months. Facial weakness, tinnitus, hearing loss, swallowing and hoarseness improved to near normal in six months.

Discussion

Immunocompromised patients are more prone to infections with unusual organisms and atypical presentations of infections by common pathogens[1,2]. Varicella zoster virus is a human herpes virus causing chickenpox as the primary infection. VZV may remain dormant in cranial nerve ganglia, dorsal root ganglia and autonomic ganglia. In a susceptible situation, it may reactivate and cause herpes zoster (shingles). When this reactivation happens in cranial nerves especially in the

facial nerve, it is called RHS[3,4]. However, the association of RHS with multiple cranial nerve involvement and persistent hiccups is less well reported. This patient had multiple cranial nerve palsies, including cranial nerve VII, VIII, IX and X with herpes zoster oticus and vesicles in the palate with varicella zoster virus infection.

The most disabling symptom was the persistent hiccups. Hiccups are usually self-limiting. When hiccup lasts more than two days, it is called persistent hiccups. When it persists for two months, it is called intractable. The most likely pathophysiology is a modulation of reflex arc involving diaphragm, phrenic and vagus nerves, sympathetic pathways and brain stem. His non-contrast MRI scan of the brain did not show any brain stem pathology. An ultrasound scan of the diaphragm did not reveal any structural abnormality or paralysis. Chest x-ray was unremarkable for lung parenchymal pathology. Serum biochemistry for serum electrolytes, corrected serum calcium, transaminases were within normal range and his serum creatinine showed mild elevation from his baseline. RHS reported with persistent and intractable hiccups are mainly due to vagus nerve involvement. In some of these case reports, hiccups have resolved with the resolution of palatal vesicles which was also observed in this patient. This may support vagus nerve involvement for the persistent hiccups in this case[9-11].

Conclusion

RHS can present as multiple cranial nerve palsies. Persistent hiccups may be caused by vagus nerve involvement in RHS. This case highlights that prompt and optimum treatment can give a favourable outcome, especially in patients with multiple comorbidities such as renal impairment and immune suppression.

Informed consent – The patient has given verbal and written consent to publish his history and images as a case report.

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Case report

Pronounced isolated severe apraxia of speech, a rare presentation of an acute ischaemic stroke

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Sri Lanka Journal of Neurology, 2021, **8**, 23-24

A 39-year-old previously healthy woman presented with sudden onset loss of speech. Except for subtle right facial asymmetry, no other neurological deficits were found. A non-contrast CT scan was unremarkable. She was thrombolised with iv alteplase (0.9mg/kg standard dose) after 2 hours from the onset.

The facial asymmetry improved over 24 hours, post thrombolysis. Her motor, sensory, coordination and cranial nerve examination were normal. She was having severe difficulty in production of speech but was able to comprehend and write normally. She could cough and produce simple monosyllable sounds and repeat the monosyllable sounds. Mild buccopharyngeal apraxia was noted in blowing. However, when she attempted to speak, it was very effortful.

Her MRI brain, which was performed after 10 days revealed T2W, FLAIR, DWI hyperintensity in left inferior frontal gyrus. However, no restricted diffusion in ADC or contrast enhancement was noted. This T2 shine through in the left inferior frontal gyrus confirmed a sub-acute infarction (Figure: MRI Brain T2W, FLAIR, DWI, ADC). Magnetic resonance angiogram of neck and brain vessels did not show any occlusions.

She was normotensive, serum cholesterol was elevated and had a normal HbA1c. ESR, CRP, complete blood counts and blood picture were normal and ANA, HIV antibodies, and VDRL were negative. Her ECG, 24-hour Holter and transthoracic echocardiogram were unremarkable. No right to left shunts were detected in transoesophageal echocardiogram. Genetic thrombophilia screening tests were negative for factor V Leiden mutation, Prothrombin 20210 gene mutation and Methylenetetrahydrofolate reductase (MTHFR) gene mutation.

Discussion

This woman presented with subtle right lower facial weakness and a speech problem as an acute ischemic stroke, and she was thrombolised in 2 hours. Her MRI brain revealed a subacute infarction in the left inferior frontal gyrus.

She had normal bulbar muscle function with normal swallowing and had normal cerebellar functions. She was not abulic since her activities were normal except for speech. Her speech disorder was considered as apraxia of speech (AOS) as her verbal output was impaired with intact repetition, and mild orobuccal apraxia.

Apraxia of speech (AOS) has emerged as the term to describe a motor speech disorder characterized by an impaired ability to coordinate the sequential, articulatory movements necessary to produce speech sounds (Wertz et al., 1984). Confusion in the literature around AOS stems from the fact that terminology associated with this disorder has varied greatly. Also, symptoms associated with AOS often co-occur or overlap with those caused by neuromuscular deficits indicative of the dysarthrias and the linguistic errors associated with aphasia. AOS is, however, a distinct motor speech disorder. Apraxia of speech is a relatively a new terminology, which is characterised by inability to motor programming and coordinating the sequence of articulatory movements[1]. The general term “apraxia” was introduced by Liepmann in 1908 and defined it as the inability perform motor tasks without impairment of muscle strength[2]. Darley in 1969 coined the term apraxia of speech for the Liepmann’s notion of “apraxia of the glosso-labio-pharyngeal structures”[3].

A similar speech disorder with presence of preserved language skills and unimpaired muscular function was described by Paul Broca in 1861. He named it as aphemia, and he localised it to a cerebral lesion.

It is important to differentiate AOS from a language disorder (aphasia) and dysarthria due to muscle weakness or incoordination. Although our patient had mild facial weakness, it fully recovered in 24 hours but her speech impairment persisted. Her comprehension and written language were preserved, so as other orobulbar muscle functions.

Neuroanatomical localization of the AOS is difficult but many studies have demonstrated a lesion in the left frontal cortex. The commonest cause of this rare phenomenon is considered to be vascular lesions.

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Tumours, trauma, and neurodegenerative disorders such as primary progressive aphasia and corticobasal degeneration are other causes[5,6].

Functional speech disorders also could mimic AOS, and this could be extremely challenging especially when in therapeutic decision making in neurological emergencies like hyperacute ischemic strokes like in our case[7].

In mildly apraxic patients, poor prosody may be the primary speech deficit and, therefore, goals designed to improve intonation and stress may be the most appropriate. Treatment of moderate and severe AOS is mainly considered to be relearning oral postures for individual speech sounds[5]. We now understand AOS to be a unique speech disorder that is distinct from other speech and language deficits such as dysarthria, aphasia or stuttering.

Our patient's stroke work up was negative for cardiac and large vessel studies and genetic thrombophilia screening. She was started on antiplatelets and moderate intensity lipid lowering treatment. She made a marked improvement in post stroke one month following speech and language therapy.

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The art of colour blind neurologist Paul Richer

Saman B. Gunatilake[1]

Sri Lanka Journal of Neurology, 2021, **8**, 25-26

Paul Marie Louis Pierre Richer was born on February 17, 1849, to a family of linen and fabric merchants in Chartres – a region in Centre-Val de Loire, south-west of Paris. When he was young, every day on his way to school, Paul would go past the famous cathedral embellished with countless figures, which stimulated his imagination. Watching the stonemasons repairing the structure, as he passed by, certainly contributed to Richer's fondness for sculpture.

Paul Richer as young medical student lacked any formal artistic training, but came to Jean-Martin Charcot's attention in 1874. Charcot claimed that Richer's drawings were accurate enough for a doctor to diagnose the illnesses depicted. That was the motivation for appointing him, in 1882, as head of the Charcot Museum at the Hôspital de la Salpêtrière. Both Charcot and Richer published a series of scientific reviews on artworks that appeared in the Iconographie de la Salpêtrière, a journal published from 1888 to 1918, and coedited by Richer himself.

Paul Richer was color blind, which explains why his work is solely composed of sketches and drawings and, later, engravings and sculptures, but never paintings.

Paul Richer's drawings. Top: Passionate attitude period – sad phase (left). Epileptiform period – phase of tonic immobility or tetanism (right). Bottom: Contortion phase l'arc de cercle (left). Prodrome – agitation and partial contractures (middle). Period of Clownism – phase of great movements (right)

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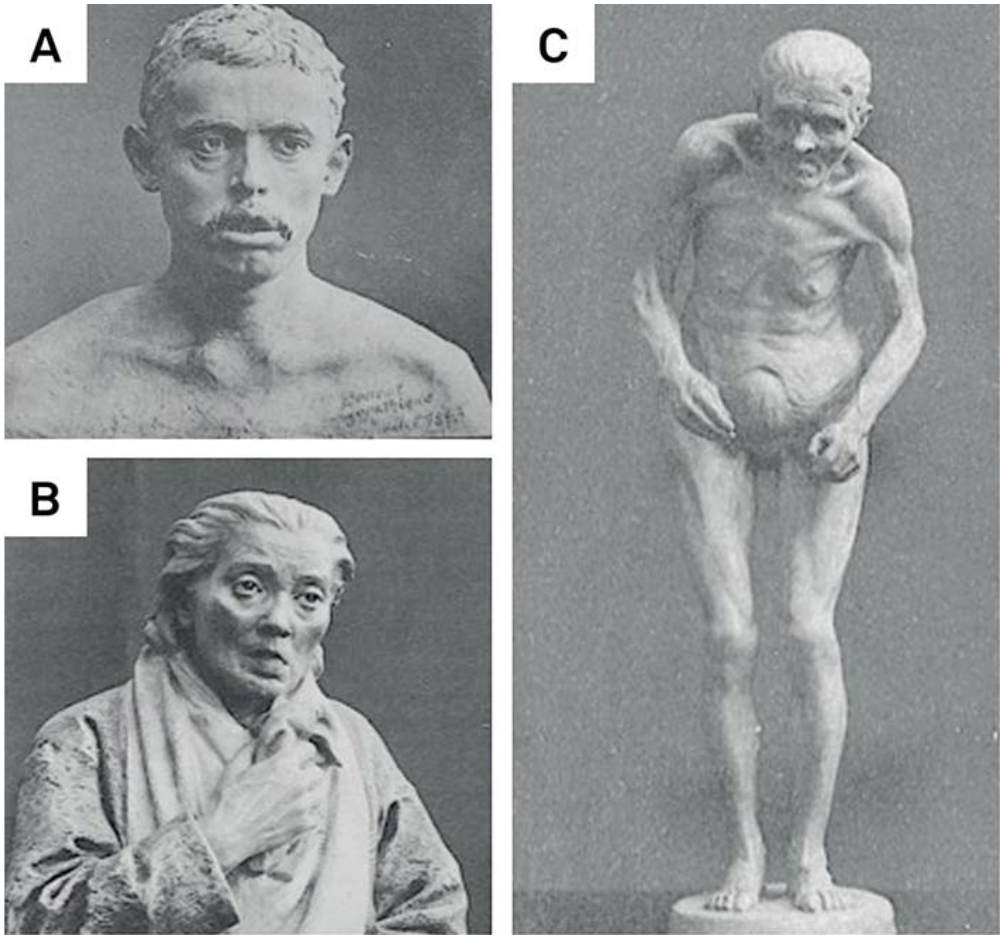
In 1893, Richer portrayed a bust of a 26-year-old man called Henri 'Bonn'. The bust of a young man suffering from myopathy illustrates a study of sufferers from amyotrophy, in which muscles waste away because the nerves supplying them are diseased (Figure A).

The woman suffering from Labio-Glosso-Laryngeal Paralysis (circa 1894), a life-size half-body plaster sculpture evokes extreme pathos (Figure B). The viewer's focus is the figure's finely-modeled face and hand, which reveal delicately-rendered veins underneath her skin, and her facial expression.

Richer's most well-known pathological sculpture portrays a woman suffering from Parkinson's Disease (Figure C). A patient called, simply, 'Gell' represents the almost-perfect clinical schema of Parkinson's Disease. In that 47 cm high sculpture, you can see the typical sufferer as having an expressionless visage, a head and torso inclined forward, a sunken chest, and flexed arms and legs: in a word, "the look of an old person who has been welded together".

Sculptures by Paul Richer: A. Bust of a young man suffering from myopathy. B. The woman suffering from Labio-Glosso-Laryngeal paralysis. C. Attitude and faces in Parkinson's disease.



Letter to Editor

Sri Lanka Journal of Neurology, 2021, **8**, 27

I have read the article 'Is testosterone a potential agent for patients with delayed recovery from Guillain-Barre' Syndrome?'[1] 'which emphasizes a very important aspect of management of Guillain Barre' syndrome (GBS). However I would like to highlight some issues in relation to this article.

1. There is a major flaw in the contents of table titled "First nerve conduction study on day 3" of the said article. The values of distal motor latencies (DML) are not shown in this table. As a consequence, the motor conduction velocities (MCV) indicated are questionable since it is not possible to calculate MCV without DML values. Latencies of sensory conduction are not presented either.

2. In the absence of DML values it is not possible to draw accurate conclusions. There is no basis for the given diagnosis of acute inflammatory demyelinating neuropathy (AIDP). In fact, the findings presented in this table are suggestive of axonal degeneration (reduced action potential amplitudes with preserved conduction velocities) rather than demyelination. There is one conduction block which is a known phenomenon in acute axonal neuropathies as has been reported in axonal GBS[2,3,4].

3. There are also many inconsistencies and deficiencies in all the tables containing NCS findings such as non-uniform labelling or unlabelling of the stimulation, recording sites and segments, empty cells without any data of which the meaning is unclear and the use of unexplained non standard abbreviations.

The above errors are misleading to the readers and can also degrade the high standards achieved by the journal. As such it is imperative that the situation with regards to those NCS tables is clarified or rectified.

Sudath Gunasekera

Consultant Clinical Neurophysiologist,
National Hospital of Sri Lanka.

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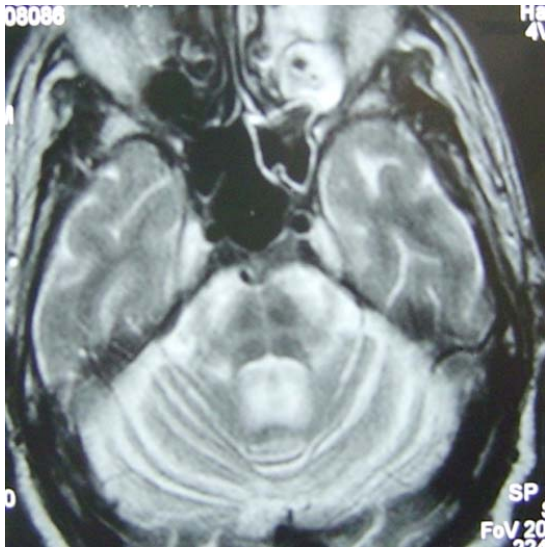
Neurology quiz

Sri Lanka Journal of Neurology, 2021, **8**, 28-30

(Compiled by Dr. A. T. Alibhoy)

1. A 35-year-old man presents with progressive ataxia, ophthalmoparesis and peripheral neuropathy. His father also suffered from a similar illness. MRI scan of the brain is shown.

What is the diagnosis?



2. A 50 year old man was observed to be seated in the outpatient department adopting this arm position.

What is this physical sign?

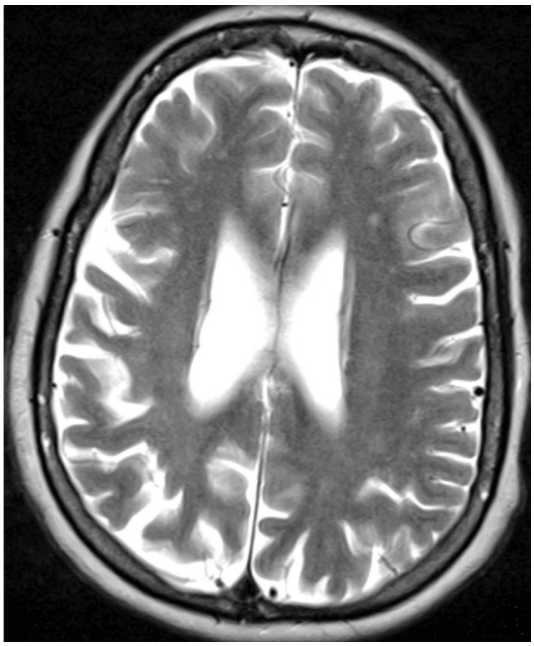
3. A 65 year old man presented with intense holocephalic headaches for the last 18 months. These headaches were triggered only by exertion like brisk walking, playing table tennis and sexual activity. The pain lasted for 15-60 min in each attack. Prior treatment with various drugs such as amitriptyline, valproate, flunirazine, paracetamol, and ibuprofen had no benefit.

Neurological examination was unremarkable. His MRI and MRA of brain showed no abnormalities. His routine ECG showed an old infarct in inferior leads. Exercise ECG test was positive and this exercise brought on the headache. He was subjected to a coronary angiogram.

What is the likely neurological diagnosis?

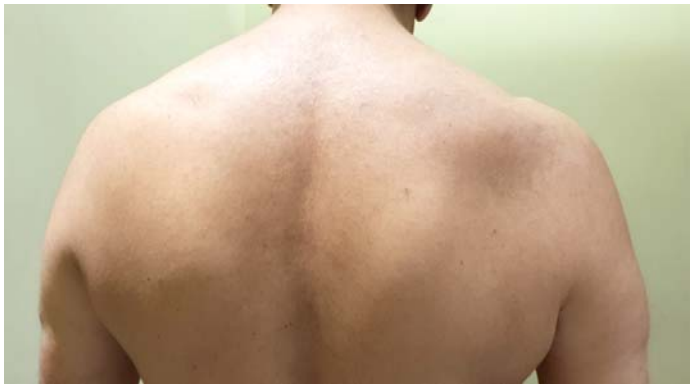
4. A 64 year old man presented with difficulty to perform voluntary movements with his left hand, which on examination showed rigidity and dystonia. MRI scan of the brain is shown.

What is the likely neurological diagnosis?

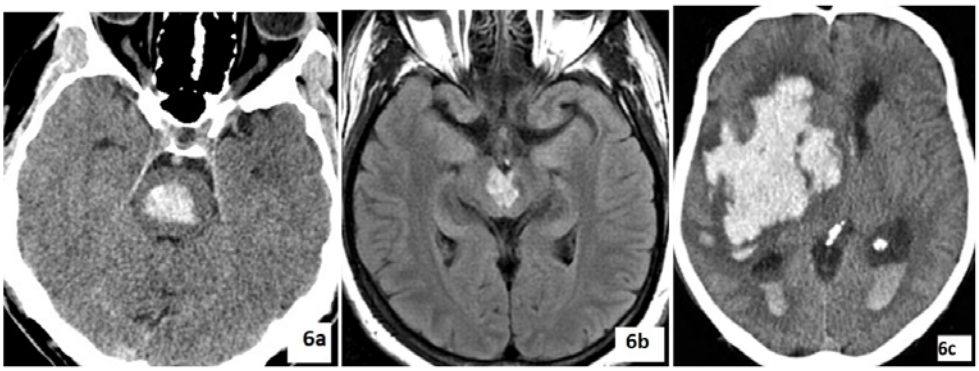


5.

a. What nerve is affected in this patient?
b. Name two sports that can cause this palsy?



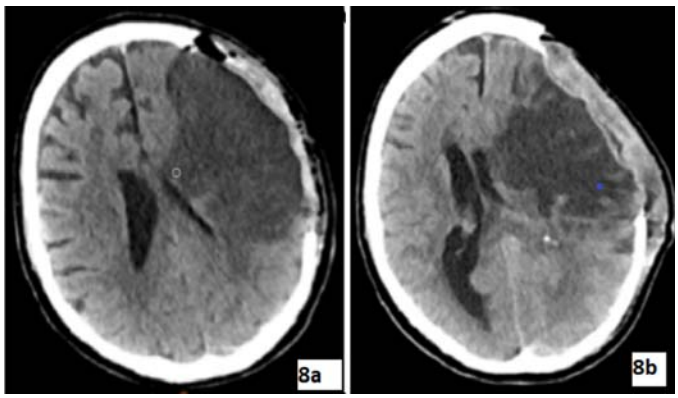
6. A 60 year old woman was found unconscious at home. She was noted to have fixed midposition pupils. Which one of the 3 CT scans is most likely to be that of this patient?



7. A 15 year old boy presented with recurrent ischemic strokes in the frontal and parietal watershed territories. Axial T1-weighted MRI showed multiple hypointensities in the basal ganglia. What radiological sign could be seen on the FLAIR MRI which is named after the creeper shown in the image?

8. A 50 year old man underwent a decompressive hemicraniectomy for a malignant middle cerebral artery infarction (Figure 8a). Three weeks after surgery, he developed a headache and became less responsive. The skin flap overlying the craniectomy became sunken. Repeat CT scan is shown (Figure 8b).

What is the likely neurological diagnosis?



(Answers on page 37)

Perspectives

COVID-19 vaccines and the risk of Bell's palsy

K P C Dalpatadu[1], T Chang[2]

Sri Lanka Journal of Neurology, 2021, **8**, 31-33

Background

Global yearly incidence of Bell's palsy varies between 15 to 30 per 100,000 persons[1] and has been reported following viral infections and immunisations[2]. Although initially thought that COVID vaccines did not confer an increased risk[3], recent studies report an increased incidence of Bell's palsy following vaccination. Which of the COVID vaccines confer a greater risk of Bell's palsy and the risk of relapse following the second vaccine dose is currently unknown. Lessons learnt from a patient presenting with vaccine related Bell's palsy and review of published literature are highlighted here to present a perspective on Bell's palsy associated with SARS-CoV-2 vaccination.

Case history

A 60-year-old healthy Sri Lankan woman developed difficulty in closing her right eye associated with right-sided facial sagging and drooling ten days after receiving the first dose of ChAdOx1-S (Covishield-Astra Zeneca vaccine). She did not have a history of fever, earache or blisters in her right ear. On examination, a right-sided lower motor neuron seventh cranial nerve palsy was evident (House-Brackmann[4] score 3). Rest of the neurological examination was normal. Nerve conduction studies confirmed a right lower motor type facial nerve palsy (right facial nerve motor conduction amplitude of 810 µV vs 1.55 mV in left, motor conduction latencies right 3.66 ms vs left 3.06 ms). Gadolinium-enhanced MRI and MRA of her brain were normal. She was treated with 1mg/kg/d of oral prednisolone for 5 days, physiotherapy and eye care. She made a full clinical recovery after one month. However, she could not have the second dose of ChAdOx1-S vaccine due to unavailability. Five months following recovery, she received two doses of inactivated SARS-CoV-2 vaccine (BBIBP-CorV:Sinopharm) 4 weeks apart without any complications.

Discussion

Occurrence of Bell's palsy 10 days after receiving the COVID vaccine in the absence of other known aetiological factors favours a diagnosis of vaccine related Bell's palsy in our patient. Although the pathophysiology of Bell's palsy following SARS-CoV-2 vaccination remains unclear, there are several postulated mechanisms. High titre of spike protein antibodies and a high CSF:serum antibody index detected in patients developing Bell's palsy after Pfizer-BioNTech mRNA vaccines[5] suggest immunological mechanisms causing facial nerve damage. Activation of interferons[5] and auto-immunity due to molecular mimicry by vaccine antigens[2], reactivation of the dormant virus within the CNS are suggested other possible mechanisms. Interestingly Bell's palsy has been reported following all types of first generation vaccines platforms currently approved for the prevention of SARS-CoV-2 infection (mRNA vaccines: Pfizer-BioNTech[6,7,8,9,10] and mRNA-1273 Moderna[3]; viral vector vaccines: ChAdOx1-S-Oxford Astra Zeneca[6,11] and Ad26.CoV2.s-Janssen[12]; and inactivated viral vaccines: Coronovac[7]). Table 1 summarizes the incidences and the risks of developing Bell's palsy related to COVID-19 infection and the different vaccine platforms.

The variations of reported incidences of Bell's palsy among the studies are likely to reflect the differences in predisposition for Bell's palsy in different settings rather than the type of vaccine platform. Although COVID vaccination appears to be associated with a higher incidence of Bell's palsy compared to that of the normal population, currently there is inadequate evidence to suggest that one vaccine poses a greater risk than another[14]. Furthermore, the risk of Bell's palsy is several fold higher following COVID-19 infection than in the normal population and after vaccination.

There is only a single case report of sequential recurrence of Bell's palsy following the first and second dosses of COVID vaccination in which the platform was a mRNA vaccine[15]. Our patient had no recurrence even though she received two further doses of COVID vaccination. The delay and the change of vaccine platform in our patient was due to logistical issues of the vaccine rollout rather than design.

Conclusions

Currently, there is not enough data to choose one vaccine over another to mitigate the risk of Bell's palsy. Vaccine associated Bell's palsy is likely to recover completely as seen in our patient despite a marked neurophysiological deficit at disease onset. The risk of recurrence with repeated doses of vaccination is likely to be low. The risk of Bell's palsy is markedly higher following COVID-19 infection than after vaccination. Given the morbidity and mortality of COVID-19 infection, the benefits of vaccination far outweigh its risks.

[1]*Department of Physiology,* [2]*Department of Clinical Medicine, Faculty of Medicine, University of Colombo, Sri Lanka.*

Table 1. Incidences and risks of Bells' palsy in relation to COVID-19 infection and currently used vaccine platforms

	Incidence of Bell's palsy	*Risk of developing Bell's palsy*	*References*
COVID-19 infection	• 82 per 100,000	• Relative risk 6.8 (95% CI=3.5-13.2, <.001)	(13)
mRNA vaccine (Pfizer)	• 89 per 100,000 per year/13.6 per million doses administered[6]	• Israel case control study: Odds ratio 0.84 (95% CI, 0.37-1.90; p=.67)[8]	(6) to (10)
	• 21 per 100,000 in phase 3 clinical trials[9,10]	• Hong Kong nested case control study: Odds ratio 1.755 [0.886-3.77]; p=0.119	
	• 42.8 per 100,000 person-years (Hong Kong)[7]		
Viral vector vaccine (Astra Zeneca)	• 4.1 per million doses administered[6]	• Data not available	(6), (11)
	• 3 in vaccine group across 4 clinical trials out of 23,745 participants[11]		
Inactivated viral vaccine (Coronovac)	• 66.9 cases per 100,000 person-years (Hong Kong)	• Hong Kong nested case control study: Odds ratio 2.385 [95% CI 1.415-4.022]; p=0.0011)	(7)
Normal population	• 15-30 per 100,000 per year		(1)

Acknowledgement

Dr Kamal Gunarathne, Consultant Clinical Neurophysiologist of the National Hospital of Sri Lanka, Colombo for the nerve conduction studies.

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Guidelines to authors

Sri Lanka Journal of Neurology, 2021, **8**, 34-36

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All articles received will be acknowledged to the corresponding author. Each manuscript will be read by the members of the editorial board to decide whether it should be further reviewed. Those selected for review may be sent anonymously to referees.

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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, in 11pt (Calibri font preferable), on 216 × 279 mm (8 × 11 in), or A4 (212 × 297 mm) size paper in Microsoft Word Software. 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.

Title page

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.
5. Name, address, e-mail and telephone number of author responsible for correspondence.
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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):

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Design setting

Patients Intervention (if any)

Measurements

Results

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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.

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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.

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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 name, giving the name and location of the manufacturer in the text in parentheses.

References

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.

The reference list should not include unpublished material. Symposium papers may be cited from published proceedings; oral presentation of a paper at a meeting does not constitute publication. References to articles or books accepted for publication but not yet published must include the title of the journal (or name of the publisher) and the year of expected publication. Unpublished work (personal communication, papers in preparation) may be cited by inserting a reference within parentheses in the text; authors must submit a letter of permission from the cited persons to cite such communications.

Sample references below are in the style required by the *SLJN*.

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

1. Standard article.

   Bernstein H, Gold H. Sodium diphenylhydantoin in the treatment of recurrent arrhythmias. *Journal of the American Medical Association* 1965; **19**1: 695-9.

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.

Other citations in Reference List:

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.

In-text citations of unpublished material (to be placed within parentheses):

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).

Tables

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.

References

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, 2021, **8**, 37-38

Answer 1

Spinocerebellar ataxia

"Hot cross bun" sign is a radiologic finding which describes a cruciate hyperintensity in the pons on axial T2W and FLAIR MRI sequences. The name of the sign is derived from a spiced sweet bun, marked with a cross at the top. It is classically described in patients with the cerebellar subtype of multiple system atrophy (MSA-C).

However, it has also been reported in spinocerebellar ataxia (SCA) 1, 2, 3, 7, and 8, progressive multifocal leukoencephalopathy, paraneoplastic cerebellar degeneration, cerebrotendinous xanthomatosis, fragile X tremor ataxia syndrome and variant Creutzfeldt-Jakob disease.

Answer 2

Shoulder abduction relief sign

Shoulder abduction relief sign refers to the posture of arm abducted at shoulder with hand rested on top of head to relieve pain. It is observed in cervical radiculopathy, in which the lower cervical roots are involved. It has a diagnostic value in pointing to possible cervical disease in patients complaining of shoulder pain.

Shoulder abduction can be used not only as a diagnostic sign but may be incorporated in the conservative management of patients suffering from cervical radiculopathy affecting the lower cervical roots.

Answer 3

Cardiac cephalalgia *"Headache of the Heart"*

This patient's headache which was induced during the stress test was completely relieved by sublingual nitroglycerine, raising the possibility of cardiac cephalalgia. His coronary angiogram revealed triple vessel disease and CABG provided complete resolution of the exertional headaches.

Cardiac cephalalgia is an uncommon presentation of coronary ischemia. It may be the only manifestation without associated chest pain, and the response to nitrates aids diagnosis. Useful clues are older age, no previous history of headache, presence of coronary artery disease risk factors, and headaches on exercise. Distinguishing this from migraine is important, as triptans are contraindicated.

Answer 4

Corticobasal degeneration

Corticobasal degeneration is a rare neurodegenerative disease with an asymmetric onset characterized by apraxia, dystonia, rigidity, akinesia, and postural instability. The axial MRI image shows a strikingly asymmetric cortical atrophy, more marked on the side contralateral to the clinical symptoms.

Answer 5

a. Suprascapular nerve

b. Overhead sports like Volleyball and Tennis

A common cause for Suprascapular neuropathy is repetitive overhead trauma. This injury is often seen in volleyball, badminton, tennis, and baseball players, weight lifters, and swimmers. These sports expose the athlete's hands to overhead, abducted and externally rotated positions for prolonged periods of time causing damage to the nerve.

Answer 6

Corticobasal degeneration

Hemorrhage into the midbrain tegmentum causes the pupils to be in midposition and fixed. Tectal hemorrhage results in fixed dilated pupils, which may also be seen in cerebral herniation. Pontine hemorrhage results in pinpoint pupils.

Answer 7

Ivy sign

Moyamoya disease is a chronic cerebrovascular disease characterized by progressive stenosis of the terminal portion of the internal carotid artery, and development of dilated collateral network at the base of the brain.

MRI scan may show cerebral infarctions commonly in the watershed territories. Axial MRI may show multiple tiny hypointensities in bilateral basal ganglia due to collateral vessels.

FLAIR MRI may demonstrate leptomeningeal high-signal intensity called the "ivy sign" which resembles creeping ivy on stones. This radiological finding is due to slow flow in engorged cortical pial arteries. This sign can also be found in the contrast enhanced MR images as diffuse leptomeningeal enhancement.

Answer 8

Syndrome of the Trephined or sinking skin flap syndrome

This syndrome usually presents within weeks to months after craniectomy. These patients develop headaches, seizures, reduced alertness and focal deficits. The symptoms may have a postural component.

When the atmospheric pressure exceeds the intracranial pressure, the skin flap presses on the brain tissue resulting in paradoxical herniation. Neuroimaging shows a depressed skin flap at the craniectomy site and concave deformity of the adjacent brain with midline shift.

The symptoms resolve promptly with Trendelenburg positioning and hydration. The definitive treatment is cranioplasty. It is important for Neurologists to be aware of this condition in view of the increasing number of their patients undergoing decompressive craniectomy especially for stroke.