Foreign accent syndrome and other neuropsychological sequelae of a parieto-occipital lesion following COVID-19 associated posterior reversible encephalopathy syndrome.

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Word Count: 4570 (excluding Abstract/Reference).

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Abstract

Objective: We describe a previously fit and well 54-year-old female who acquired a range of severe and persisting neuropsychological impairments following a posterior reversible encephalopathy syndrome (PRES) complication of COVID-19. The initial presentation included aphasia, a neurogenic foreign accent syndrome (FAS) and a persisting complete cortical blindness from the underpinning parieto-occipital brain injury.

Method: Neuropsychological single clinical case report.

Results: The patient retained insight and made good early progress with their adjustment to the numerous losses caused by the COVID-19 associated acquired brain injury. Comprehensive neuropsychological investigation characterised an acalculia, along with deficits in focused, sustained and divided attention impacting on verbal memory, working memory and executive functioning, amongst numerous relative strengths.

Conclusion: Similar to PRES from other aetiologies, COVID-19 associated PRES can in some cases cause irreversible acquired brain injury. The diverse neuropsychological effects need to be comprehensively investigated and managed. This case adds to the neuropsychological literature on PRES, FAS and acquired brain injury as a rare complication of SARS-CoV-2.

Keywords: Posterior Reversible Encephalopathy Syndrome, Foreign Accent Syndrome, COVID-19, Acalculia, Acquired Brain Injury.

Introduction

It is well established that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can cause neurological symptoms such as headache, anosmia and ageusia, but in rare cases, may also lead to severe neurological syndromes via direct and indirect neuropathological mechanisms (Asadi-Pooya & Simani, 2020; Cataldi et al., 2020; Pleasure et al., 2020; Zubair et al., 2020).

In an early study of 214 COVID-19 inpatients in Wuhan, Mao and colleagues (2020) reported that 36.4% experienced neurological complications such as cerebrovascular disease. Scullen and colleagues (2020) described a sample of 76 New Orleans critical-care inpatients with COVID-19 associated neurological conditions including encephalopathy (74%), acute necrotising encephalopathy (7%) and vasculopathy (19%). Other presentations have included encephalitis (e.g., Filatov et al., 2020), motor peripheral neuropathy (Abdelnour et al., 2020), Guillain Barre Syndrome (Ottaviani et al., 2020), and basal ganglia haemorrhage (Haddadi et al., 2020). The UK CORONERVE study (Varatharaj et al., 2020) reported 125 severe neurological cases characterised by cerebrovascular events (62%), unspecified encephalopathy (23%), encephalitis (18%), and cerebral vasculitis (1%). This is consistent with the understanding that cerebrovascular conditions such as stroke (e.g., Agarwal et al., 2020; Sharifi-Razavi et al., 2021) are the most prevalent mechanism cause of COVID-19 associated brain injury.

Notably, the clinical literature is limited by an absence of comprehensive cognitive investigations leading to only sparse neuropsychological knowledge. However, it is likely that the neuropsychological profiles will be variable, heterogeneous, and dependent on the unique pattern of injury (Wilson et al., 2020). One example is the case of Balint's Syndrome secondary to COVID-19 associated stroke (Narayanan et al, 2020).

Posterior reversible encephalopathy syndrome (PRES)

Posterior reversible encephalopathy syndrome (PRES) is a rare neurological complication of severe COVID-19 infection, most frequently within hospitalised patients (Doo et al., 2021; Elhassan et al., 2020; Kaya et al., 2020; Kishfy et al., 2020; Wijeratne et al., 2021). Originally classified by Hinchey and colleagues (1996), PRES is a frequently reversible neurovascular syndrome which presents with symptoms such as headache, seizures, other focal neurological deficits (e.g., aphasia), altered consciousness, and visual symptoms ranging from blurred vision to complete cortical blindness (Bartynski, 2008; Fischer & Schmutzhard, 2017).

On neuroimaging PRES characteristically shows diffuse vasogenic oedema that can occur anteriorly, but most frequently in the posterior vascular watershed areas within the parietal and occipital lobes due to the vulnerability of the underpinning vasculature (Bartynski, 2008; Fischer & Schmutzhard, 2017). However, there is significant heterogeneity. Bartynski and Boardman (2007) reported high variance in a review of neuroimaging from 136 PRES patients and identified three

primary patterns of vasogenic lesion; 1) holohemispheric (frontal, parietal, occipital with lesser involvement of temporal, 23%), 2) superior frontal sulcus (27%), 3) dominant parietal-occipital (with variable involvement of temporal lobes, 22%) with a fourth partial or incomplete expression of PRES (28%).

Risk factors for PRES include hypertension, renal disease, certain immunomodulatory therapies, autoimmune conditions, some chemotherapeutic medications, and sepsis (Bartynski, 2008; Fugate et al., 2010). Although PRES has been well described, the aetiology remains unclear. There is considerable evidence that PRES arises from a severe hypertensive episode disrupting cerebral autoregulation leading to brain hyper-perfusion, but also accounts of PRES occurring without hypertension (Bartynski, 2008; Bartynski & Boardman, 2007). An alternative hypothesis is that PRES results from endothelial dysfunction in a systemic inflammatory response (Bartynski, 2008; Bartynski & Boardman, 2007). Overall, there are numerous clinical situations where both causal routes appear to be involved (Fischer & Schmutzhard, 2017) with the aetiology believed to be frequently "multifactorial" (Hinchey et al, 1996, p. 499).

PRES is believed to be an under-reported condition with the true prevalence of COVID-19 associated PRES unclear (Iftikhar et al, 2021). Yeahia et al (2021) reviewed neuroimaging from thirty cases and found that prior to PRES, 80% experienced severe COVID-19 symptoms requiring ventilation, with an acute hypertensive episode in 73%, with PRES presenting with altered mental status (83%), visual changes (45%) and seizures (42%). Iftikhar et al (2021) undertook a further review of fifty-six cases and highlighted that consistent with previous findings on PRES following other conditions (Alshami et al., 2021; Lifson et al., 2019), most cases did not initially present with visual disturbance.

When PRES is detected and treated early, it can often be reversible with only transient effects, including after COVID-19 (e.g., Kaya et al., 2020). However, PRES can also result in serious irreversible neurological outcomes including mortality, particularly if there has been a haemorrhagic component (Alhilali et al., 2014). Notably, although Yeahia et al, (2021) acknowledge that valid comparison of PRES arising from other conditions and from COVID-19 is challenging due to variance between studies, there is a suspicion that PRES may present with increased risk of haemorrhage after COVID-19 (Iftikhar et al, 2021; Yeahia et al, 2021). When PRES is irreversible the pattern of acquired brain injury can include persisting visual impairments, and cognitive difficulties in domains such as visuospatial, attention and executive functioning (Bartynski & Boardman, 2007; Stevens & Heran, 2012; Stroescu et al., 2011). However, the PRES neuropsychological knowledge base is sparse. Alshami and colleagues (2021) reported patient outcomes from a large review of hospitalised PRES cases (N = 635), which included 2% mortality, 67% discharged home, and 18% experiencing ongoing difficulties which required further care. Iftikhar et al (2021) reported that only 42% of COVID-19 related PRES cases achieved a full medical recovery, with 35% a partial recovery, and 12% mortality within two to four weeks of PRES.

Foreign accent syndrome (FAS)

PRES clearly has the potential to cause varied neuropsychological presentations, yet to our knowledge there have been no documented cases of Foreign Accent Syndrome (FAS). FAS is "a relatively rare motor speech disorder characterized by speech errors which are perceived as a foreign accent by members of the same language community" (Marien et al., 2019, p. 94). In 1907 Pierre Marie documented a left hemisphere stroke patient who experienced a profound change in accent, with over 150 case reports since (Marien at al., 2019; Verhoeven & Marien, 2010). Whitaker (1982) operationalised FAS into four criteria; 1) the accent is considered by the patient and others to sound 'foreign' 2) the accent is unlike the patient's native dialect prior to the cerebral insult 3) it is clearly related to central nervous system damage 4) there is no evidence in the patient's background of being a speaker of the language. Following a comprehensive review of 112 cases, Marien and colleagues (2019) noted that FAS most frequently followed stroke (53%), and less frequently; trauma (13%), functional origins (5%), tumour (2%), multiple sclerosis (2%), and other neurological conditions. Onset of FAS most frequently occurred in adulthood (97%), and although not fully understood, presented more in females (67%) than males.

Reliably and validly distinguising FAS from other speech disorders such as ataxia of speech, and cerebellar ataxic dysarthria remains controversial due to the overlap in phenomenology of speech errors and because they can present comorbidly (Marien et al., 2019; Ryalls & Miller, 2014). The subjective nature of 'foreign' and Whitaker's first criteria; (i.e., the accent is considered by the patient and others to sound 'foreign') have been questioned. Marien and colleagues (2019) cite Nielsen & McKeown (1961) who postulated that the speech errors in FAS arise from a dysarthria unless the dysprosody *happens* to resemble a language to the listener. Marien and colleagues (2019) concluded that there is evidence that FAS involves both articulatory planning deficits and executive deficits from disruption to shared neural networks that can also result in ataxia of speech and ataxic dysarthria. This may explain the comorbid speech and language disorders in FAS and reinforces that the most distinguishing feature, which cannot be claimed to be consistently present in other speech disorders is the perception of the listener that the person's accent has distinctly changed to resemble another accent.

Verhoeven and Marien (2010) conceptualised three subtypes of FAS defined by the underpinning aetiology; 1) neurogenic (organic neurological damage), 2) psychogenic (associated with conversion disorder) and 3) mixed FAS (initially neurogenic followed by a functional exacerbation). Notably, the term 'psychogenic' has since been re-conceptualised as functional FAS to refer to cases of a clear psychological origin, and where organic neurological disorder triggers a conversion reaction resulting in a functional FAS overlay (Marien et al., 2019). Typically, FAS is persistent, with Marien and colleagues (2019) reporting recovery of the original accent in only 24% of those with organic neurogenic FAS (n = 87), and in 38% of functional FAS (n = 18).

Within organic neurogenic FAS the underpinning lesion locations most commonly arise from supratentorial left hemisphere lesions and rarely from right hemisphere lesions (Marien et al., 2019). Notably, organic neurogenic FAS frequently emerges following multiple lesion sites which likely relates to the finding that broad cognitive comorbidities are common in areas such as attention, acalculia, verbal memory, working memory, and executive functioning (Marien et al., 2019; Verhoeven and Marien, 2010). Although Marien et al (2019) reported that only 15% of the vascular organic neurogenic FAS cases had documented cognitive difficulties, this is potentially an underrepresentation when considering only 45% of the case reports included cognitive investigations.

In this case report we describe a patient who developed PRES with persistent and debilitating neuropsychological consequences, including aphasia, FAS, and acalculia, alongside a persistent complete cortical blindness following a severe presentation of COVID-19. In a separate paper, Elhassan and colleagues (2020) provide a detailed account of the cortical blindness. The current report provides a comprehensive neuropsychological account of the brain injury to add to the knowledge base on PRES, FAS and COVID-19-associated acquired brain injury.

Clinical case report

Ethical considerations

The patient provided valid informed consent to the use of their case in publication, with dissemination approved by the host organisation information governance department.

COVID-19 associated PRES

The patient was a 54-year-old White British female who was admitted to hospital during the first UK wave of the pandemic with a positive SARS-COV-2 PCR. This followed ten-days of fever, cough and myalgia, and two days of worsening breathlessness (admission: temperature 38.2 ºC, pulse 114 bpm and blood pressure 125/78 mmHg, initial oxygen saturations were 82% on room air). They were right-handed with a neuro-typical developmental history and aside from being an ex-smoker had no known premorbid health conditions.

Following increasing oxygen requirements, non-invasive ventilation was commenced. Lymphopenia (0.9 x10^9/l) was detected with an otherwise normal full blood count. Chest X-ray confirmed bi-basal consolidation. Oxygen requirements increased and on day 10 the patient was intubated and ventilated in response to acute respiratory distress syndrome. A diagnosis of Systemic Inflammatory Response Syndrome was made, and empirical broad-spectrum antibiotics were commenced. On day 21 of the admission, the patient had a self-terminating generalised tonic-clonic seizure with a second generalised seizure the next day. Blood pressure was briefly raised to 190/90 mmHg but otherwise remained in the normal range. A CT brain

scan (Figure 1) showed significant posterior oedema involving the occipital lobes with relative effacement of adjacent sulci characteristic of PRES.

Over the next 10 days the patient stabilised, was extubated and became progressively more orientated and aware. Although pupil responses to light were normal and fundoscopy unremarkable, neurological examination revealed a complete cortical blindness. The patient initially had poor insight into the extent of the visual impairment, including the presence of visual hallucinations at the time. The MRI brain scan (Figure 2) eight weeks after the initial admission recorded bilateral occipital cortical signal abnormalities representing cortical pseudo-laminar necrosis as a sequela of PRES. Subsequent analysis also suggested left parietal abnormalities with neurological examination suggesting parietal cortical involvement. Once medically stable, the patient was transferred to the inpatient neurorehabilitation unit approximately ten weeks after the initial admission. There was general physical de-conditioning from the critical care admission and an initial right upper limb apraxia which quickly resolved. The patient accessed multidisciplinary assessment and neurorehabilitation which included speech and language therapy, neuro-physiotherapy and neuropsychology.

FAS

The assessments recorded an acquired aphasia characterised by slowed and effortful speech, word retrieval difficulties, distorted vowel sounds, and atypical prolongation. There were also changes to speech rhythm, with altered word stress, and unexpected or exaggerated rises and falls in intonation. Strikingly, although the patient was previously a native, monolingual English speaker without a strong regional accent, clinical staff and the patient's family now experienced her as a non-native speaker. Some listeners said the patient's new accent sounded Malaysian yet the majority said it sounded Welsh, highlighting the subjective nature of accent interpretation in FAS. Notably, the patient did not speak Welsh and had no personal associations with the Welsh language or country. Over the course of care the accent remained consistent, without remission, and although the patient was aware they were unable to modify their accent on request.

Insight and neuropsychological adjustment

The patient showed good insight into their difficulties and demonstrated a remarkable resilience with signs of effective coping throughout the early adjustment, frequently describing that despite their losses they felt extremely lucky to have survived. They did not report feeling depressed or anxious and surprisingly given their prolonged intensive care, did not describe post-traumatic stress symptoms. The patient was remarkably motivated to overcome their difficulties including wishing to access the appropriate sensory support team to overcome the visual impairment and rehabilitate in the community.

Premorbid Functioning

The patient's premorbid ability fell within the 'Average' range based on educational and occupational history, supported by hold test results that were not invalidated by the cortical blindness (i.e., Wechsler Adult Intelligence Scale– Fourth Edition, WAIS-IV, Vocabulary, Scaled Score, SS = 10).

Orientation

The patient was well orientated to space and mostly to time, except for frequent date errors. Although they were generally well orientated to person, recalling their address, including the letters of their postcode, they could not recall the numbers. There were further examples of difficulty recalling personal numerical semantic information such as not being able to recall their phone number and recalling the letters but not the numbers from their National Insurance number.

Verbal memory

Although clearly reduced and less efficient, the patient's verbal memory was a relative strength, consistent with their account of memory being least affected. Although list-learning did show cumulative learning, there was inefficient registration and reduced immediate recall (Repeatable Battery for Assessment of Neuropsychological Status, RBANS List Learning, SS 4; BIRT Memory and Information Processing Battery, BMIPB Total List Learning 10th to 25th percentile; BMIPB List B 2nd to 5th percentile) with story memory particularly reduced (RBANS Story Memory SS 2). Verbal memory recognition was more preserved (RBANS List Recognition 26th to 50th; BMIPB Total Word Recognition 25th to 50th, BMIPB Total List Recognition 25th to 50th). Although weaker in delayed story memory (Story Recall SS 5), there was a stronger delayed list recall performance (RBANS List Recall >75th percentile; BMIPB A6 50th percentile) which likely reflected the impact of reduced information-processing speed on registration and recall during the initial list learning trials.

Visuospatial functioning

Although it was not possible to administer most visuospatial tests because of the cortical blindness, clock and shape drawings, along with the patient's writing did not suggest any specific visuospatial difficulties that were not explained by the visual impairment.

Language

Albeit effortful, the patient could copy and freely generate written sentences. However, even when accounting for the cortical blindness there was evidence of dysgraphia with frequent spelling errors with the patient describing difficulty 'seeing' the word in mind. Semantic ability was inconsistent (RBANS Semantic Fluency SS 4; Animals SS 9) and undermined by reduced word-finding and speed of generativity. There were strengths in verbal comprehension and concept formation (WAIS-IV Vocabulary SS 10) and retrieval and expression of verbal crystallized knowledge (WAIS-IV Information SS 13).

Attention and executive functioning

On tests of forward digit span the patient could accurately recall some of the numerical string yet with sequencing errors and a clearly reduced span, suggesting reduced auditory focused attention (RBANS Digit Span SS 4; WAIS-IV Digit Span SS 2, LDSF = 4). These difficulties clearly undermined working memory on backwards digit-span (WAIS-IV LDSB = 3 digits), during digit-span sequencing (WAIS-IV LDSS = 2) and when alternating between letters and numbers (WAIS-IV Letter-Number Sequencing SS 1, LLNS = 2 digits).

With regards to sustained attention, the patient noticed that they could count up to 10 but not to 20. Further assessment showed that they could effortfully count down from 10 to 1, but 20 to 1 was not possible. The patient could also only recite the alphabet to the letter 'T' again referring to not being able to "see" the information in mind. Notably, sustained attention was more preserved at a low cognitive load (Short Parallel Assessment of Neuropsychological Status, SPANS, Sustained and Divided Attention: Round 1) but increased demand (Sustained and Divided Attention Round 2) revealed marked difficulties with divided attention.

Consistent with the general difficulty processing numbers, the patient had noticed that they were now unable to do mental arithmetic. Serial subtractions in '3s' was prominently reduced (SPANS, Counting Backwards), with floor level WAIS-IV Arithmetic (SS 1). Although everyday calculations were reduced (SPANS Monetary Calculations, Bank Note 0/2; Change 0/2), the Numerical Activities of Daily Living scale (NADL – Informal; Measure 0/1, Transportation 1/1, Communication 0/1; General Knowledge 5/7, Money 2/3) recorded preserved strengths in some numerical knowledge. To the patient's surprise, this also highlighted that they were no longer able to understand or define 'percentage' and could not execute this operation. Although the performance on the NADL – Formal was lower than would be expected for premorbid functioning (Addition 6/6; Subtraction 4/6; Multiplication 5/6; Total 15/18), in stark contrast to WAIS-IV Arithmetic, the patient could effortfully solve some of the problems. This is likely explained by the NADL – Formal items consisting of pure arithmetic problems (e.g., what is 5 + 2?) without the need to manage the additional narrative information

present in WAIS-IV Arithmetic, which arguably increases cognitive load and executive functioning demand.

Strengths were recorded in other areas of executive functioning such as in verbal concept formation/problem-solving (WAIS-IV Similarities SS 10), and abstract reasoning (Delis-Kaplan Executive Functioning System, DKEFS, Proverbs SS 10). Reduced word generativity was recorded (F'A'S, SS 6) consistent with the aphasic word-finding difficulty.

Information-processing speed

Processing speed appeared reduced during timed tests. Cortical blindness prevented assessment of processing speed using conventional methods such as digit-symbol coding and number cancellation and given the numerical difficulties the patient could not complete Oral Trail Making (A & B).

Performance validity

There were no signs of suboptimal test engagement with no known potential secondary gain. However, it was not possible to accurately assess performance validity due to the impact of the cortical blindness and reduced auditory attention on the available formal and embedded effort tests (e.g., WAIS-IV Reliable Digit Span, RBANS Effort Index).

Discussion

Following clinical deterioration into COVID-19 associated PRES the patient acquired a posterior parieto-occipital brain injury and extensive neuropsychological difficulties. One of the most obvious changes to the patient and their family was the radically different accent. Notably, the new accent could not be explained as the result of the ventilation or intubation and appeared to present only after the brain injury. Thus, the Whitaker (1982) criteria for FAS were met - 1) the accent is considered by the patient and others to sound 'foreign' 2) the accent is unlike the patient's native dialect prior to the cerebral insult 3) it is clearly related to central nervous system damage 4) there is no evidence in the patient's background of being a speaker of the language. Consistent with findings elsewhere (e.g., Marien et al., 2019; Verhoeven & Marien, 2010), this was not an isolated impairment with the comorbid aphasia. Albeit controversial due to the subjective nature of accent interpretation (e.g., Nielsen & McKeown, 1961), the characteristic presence of the altered perceived accent was a defining feature that is not present in other acquired speech disorders.

There is increasing recognition of functional FAS, whether of psychogenic onset, or functional overlay (Katz et al., 2008; Verhoeven & Marien, 2010). Positive features of functional FAS include accent inconsistency, ability to mimic other accents, and periods of transient recovery of premorbid accent (McWhirter et al, 2019). In the current case, the new accent presented consistently in all contexts,

the patient could not mimic other accents, there was no remission with premorbid accent return, and the accent was perceived by the patient and many other listeners, which would not be consistent with functional FAS. Notably, the current case is not the first documented change in accent following COVID-19. Cotelli and colleagues (2020) described a forty-eight-year-old who developed word-finding difficulties, effortful speech and lost their Italian regional accent. However, it is unclear based on the available information whether this case met the criteria for FAS (i.e., unknown whether the change in accent sounded 'foreign' to the patient and others, Whitaker's first criterion). If so, this case may be an example of functional FAS following COVID-19 given the change was not preceded by an organic neurological condition.

With few published cognitive investigations, neuropsychological comorbidities may potentially be underrecognized in organic neurogenic FAS with the true prevalence unknown, possibly from a diagnostic overshadowing of the speech presentation. Similar to some documented FAS cases (Marien et al., 2019), the current patient presented with a range of neuropsychological impairments, most prominently in expressive language, sustained and divided attention, and in numerical processing. This was most evident on tests that required mental sequencing, even at a modest cognitive load. The test findings and the patient's accounts suggest difficulty generating and manipulating information in mind disrupting working memory and executive functioning and undermining a broad range of abilities including arithmetic.

Ardila and Rosselli (2002) suggest that there are a wide variety of neuropathophysiological routes to problems with numerical competence (acalculia) - "It is usually assumed that acalculia can result from either a primary defect in computational abilities (primary acalculia) or a diversity of cognitive defects (language, memory, etc.) impairing normal performance in calculation tests," p. 200). The patient's difficulties - comprised of problems recalling personal numerical semantic information (but not personal linguistic information), reduced numerical conceptual knowledge and impairment of arithmetic – are perhaps best explained as the impact of the range of cognitive impairments including reduced attention on working memory and executive functioning. Notably, acalculia has historically been considered a symptom of Gerstmann's Syndrome (Ardila, 2014), defined by a tetrad of finger agnosia, left-right disorientation, acalculia and dysgraphia and repeatedly associated with left parietal lesions (Pyrtek et al., 2020). The current presentation included acalculia and dysgraphia but not finger agnosia or left-right disorientation. Although this could be potentially viewed as an incomplete Gerstmann's Syndrome, the validity of this diagnostic construct is much debated, and the current case demonstrates more extensive neuropsychological deficits.

As in the current case, FAS has been previously described with acalculia. Marien et al (2019) documented that of sixty reviewed cases of vascular neurogenic FAS 15% had documented cognitive impairments such as manifestations of acalculia, difficulties with verbal memory, attention and working memory. Similar to the current case, Pyun et al (2013) described a case with acalculia and dysgraphia, but from left basal ganglia haemorrhage, exemplifying the diverse neuropathological routes to similar

impairment. This variance in lesion location causing varying manifestations of acalculia occurs elsewhere in the sparse literature on the cognitive comorbidities of FAS, suggesting there are numerous direct and indirect routes to left parietal disruption. Marien et al (2019) conclude that neurogenic FAS and its cognitive comorbidities present following left hemisphere frontoparietal or basal ganglia damage, which is consistent with the consequences of the parieto-occipital injury in the current case. Notably, in the current case it is unlikely that the occipital injury directly caused the neurogenic FAS with a lack of any indicative published examples, yet this injury most likely caused the cortical blindness (Elhassan et al., 2020).

Albeit reversible in many cases (Bartynski, 2008; Fischer & Schmutzhard, 2017), including after COVID-19 (e.g., Kaya et al., 2020) the current case provides a further example of the potential for PRES to lead to severe brain injury. This highlights how the reversibility suggested by the PRES diagnostic term can be extremely misleading. Indeed, the patient described the diagnosis to be confusing and disconcerting given the persisting symptoms, with this discrepancy likely impacting on their ongoing progress with adjustment.

When considering the three primary patterns of PRES and the significant underpinning heterogeneity of cerebral lesion location (Bartynski & Boardman, 2007), the current presentation would appear to be consistent with the dominant parietal-occipital pattern. It is important to acknowledge that in such a severe case of PRES it is not possible to rule out frontal or temporal lobe involvement even with an absence on neuroimaging. However, the cognitive tests did not suggest major frontal (e.g., dysexecutive syndrome) or temporal dysfunction (e.g., amnesic reduced verbal memory storage) with all findings on balance explained by the parieto-occipital injury and its impact on associated neural networks.

This case adds to the growing literature on COVID-19 associated PRES and highlights a further case of only partial recovery, alongside five cases of neuropsychological impairment such as ongoing visual deficits, persistent inattention, and mild cognitive deficit including temporal disorientation (Iftikhar et al, 2021). There is the clinical suspicion that COVID-19 associated PRES is more likely to result in haemorrhagic complications (e.g., Iftikhar et al 2021; Yeahia et al., 2021) associated with poorer patient outcomes (Alhalali et al., 2014), making it potentially more debilitating. In the current case, there was no clear haemorrhagic complication and even when considering the severe brain injury, there was no finding to suggest this case had an atypical neuropathological course to PRES caused by different clinical circumstances. Further research is required to determine if there are any differences between PRES and COVID-19 associated PRES.

The aetiology of PRES has historically been viewed as “multifactorial” (Hinchey et al, 1996, p. 499) as it can occur in a range of situations such as in acute hypertension and sepsis (Fugate et al., 2010) via mechanisms of disrupted cerebral autoregulation and/or endothelial damage (Fischer & Schmutzhard, 2017). Iftikhar et al. (2021) concluded that it is likely that COVID-19 adds an additional risk factor to those who are already predisposed to developing PRES, postulating that COVID-19 can

cause endothelial damage leading to PRES via mechanisms such as cytokine storm, ACE-2 receptor binding, and/or other neurotropic mechanisms. In the current case, as described by Elhassan et al (2020), blood pressure was within normal limits, suggesting that PRES was not caused by hypertension, similar to two cases documented by Kishfy and colleagues (2020). However, sepsis was a complication in the current case, and therefore endothelial dysfunction may have occurred in a potential synergistic effect with COVID-19, causing PRES.

This case adds a further account to the literature on COVID-19-associated acquired brain injury. The current presentation is consistent with the finding that the most common severe neurological complications after COVID-19 are cerebrovascular conditions, and most frequently stroke (e.g., Agarwal et al., 2020; Sharifi-Razavi et al., 2021). Consistent with Wilson et al (2020), the current case suggests that the neuropsychological profile is dependent on the underpinning injury and impact on associated networks. In this, the parieto-occipital injuries led to cortical blindness, aphasia, neurogenic FAS, and an acalculia presentation, within a profile of reduced attention disrupting verbal memory, working memory and executive functioning. It is important to highlight that without the comprehensive neuropsychological investigation, in-line with the sparse cognitive investigations in the FAS, PRES and COVID-19 associated brain injury literature, the severe cognitive difficulties would not have been effectively diagnosed and understood by the clinical team and most importantly, the patient and their family towards an informed course of neuropsychological rehabilitation.

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Acknowledgements: We would like to sincerely thank the patient for their consent and permission to publish. We would also like to thank the Neurorehabilitation team, Dr Peter Kralt (Consultant Neuroradiologist) and Dr Jason Price (Consultant Neuropsychologist).

Declaration of Interest: None disclosed.

Figure 1**.** CT brain scan showing significant posterior oedema involving the occipital lobes with relative effacement of adjacent sulci characteristic of Posterior Reversible Encephalopathy Syndrome (PRES).

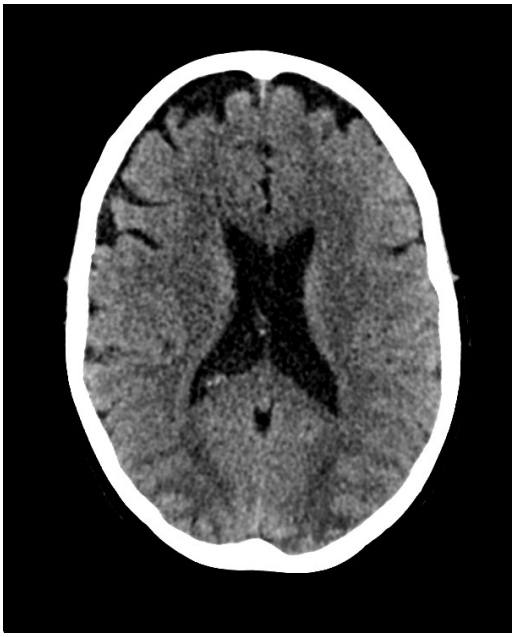
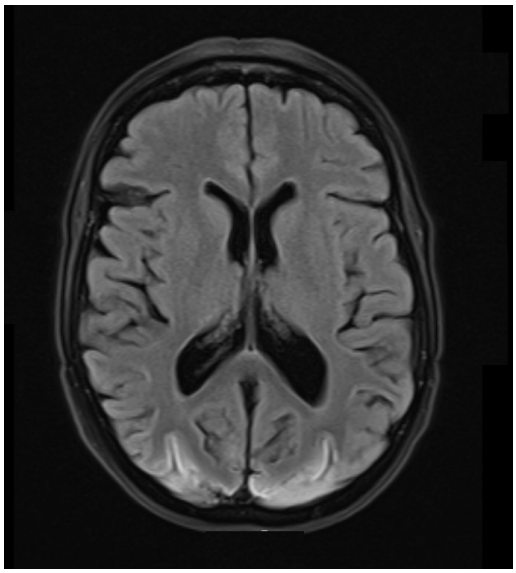


Figure 2. MRI brain scan showing bilateral occipital cortical signal abnormalities representing cortical pseudo-laminar necrosis as a sequelae of PRES.



Clinical recommendations

1. PRES is a rare complication of severe COVID-19 and should be considered in the differential diagnosis of the neurologically deteriorating COVID-19 patient.

2. Albeit frequently reversible, PRES can result in severe irreversible brain injury in some cases. Caution is recommended when providing and explaining this diagnosis to patients and their families given the potential for PRES to lead to irreversible complications that can severely disrupt the patient's functioning and challenge their neuropsychological adjustment.

3. Acquired brain injury secondary to PRES should be investigated with comprehensive cognitive assessment given the potential for diverse neuropsychological impairments (e.g., organic neurogenic FAS, acalculia, reduced attention, executive dysfunction) that can have a major impact on the patient's wellbeing and activities of daily living, requiring neurorehabilitation.

4. Increased development is required in formal and embedded effort test procedures to enable a method of validly assessing performance validity in challenging clinical situations where there is visual and attention impairment and conventional formal and embedded measures are not suitable.