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Press Case Study Article

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Could Heritable Disorders of Connective Tissue (HCTDs) Contribute to The Development of Posterior Reversible Encephalopathic Syndrome (PRES)? – A Case Study and Discussion

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Abstract

A female Caucasian patient in her early twenties presented to the authors' rural emergency department with right upper quardrant pain. On examination incidental findings Suggested features of a Heritable Disorder of Connective Tissue (HCTD) and a history of the unusual condition of recurrent Posterior Reversible Encephalopathic Syndrome (PRES) prompted the authors to consider whether these conditions could possibly be related. A number of mechanisms in disorders of connective tissue weakness might contribute to loss of autoregulation and brain hyperperfusion, or hypoperfusion, endothelial dysregulation and brain oedema from dysfunction of the blood brain barrier resulting in PRES, however there is a paucity of research on the relationship between HCTDs, PRES and BBB dysfunction. Further research to establish whether there is a connection between POTS, autonomic dysfunction, EDS/HSD and other HCTDs is required as the presence of these conditions might be underdiagnosed in patients presenting with PRES.

1. Introduction

A female Caucasian patient in her early twenties presented to the authors' rural emergency department with RUQ pain. She was diagnosed with biliary colic in the context of known cholelithiasis. The complexity of the patient's past medical history caught the attention of the primary author who recognised the presence of a possible Heritable Disorder of Connective Tissue (HCTD). Notably, the patient had previously developed Posterior Reversible Encephalopathic Syndrome (PRES) following surgery that resulted in permanent blindness. Examination revealed several features consistent with possible connective tissue weakness and the patient was referred to genetic services for genetic counselling and testing. Due to multiple complex comorbidities the presence of a connective tissue disorder had been overlooked previously. Here the authors discuss whether a Heritable Disorder of Connective Tissue could be responsible for the patient's development of PRES.

PRES, also known as Reversible Posterior Leukoencephalopathy Syndrome was first described in 1996 [1]. Diagnosing PRES relies on a combination of clinical and radiological features[2, 3, 4].

As a relatively rare condition, the incidence of PRES remains unknown. It is likely the syndrome is underdiagnosed due to lack of knowledge and challenges in diagnostic workup.

The name PRES is partially misleading as the syndrome is not always reversible and is not always confined to the posterior areas of the brain [5, 6].

PRES is associated with a number of medical conditions. The relationship between rheumatic diseases and PRES is well established in the literature [7]. It has also been reported as the presenting feature of mixed connective tissue disease in a number of case reports [7, 8].

Autoimmune disorders have been reported in up to 45% of patients who develop PRES [3]. These disorders include collagen vascular diseases, Thrombotic Thrombocytopenic Purpura (TTP), the vasculitides, cryoglobulinemia, Inflammatory Bowel Disease (IBD), Rheumatoid Arthritis (RA), Primary Sjögren's Syndrome (pSS), and Neuromyelitis Optica Spectrum Disorders (NSOD) [6].

PRES has been reported in association with defects in the Col4A1 gene, notably the Hereditary angiopathy with Nephropathy,

Aneurysms, and Muscle Cramps (HANAC) syndrome, which results in fragile blood vessel architecture (Plaiser, et al, 2007). To date, no reports on PRES in connection with other HCTDs such as the hypermobility spectrum disorders (HSD), or Ehlers Danlos Syndrome (EDS) exist to the authors' knowledge.

Eclampsia, chronic renal failure, haemolytic uremic syndrome, hypercoagulable states and Covid 19 infection are some other medical conditions associated with development of PRES [9].

Use of immunosuppressive and cytotoxic medications has been cited in literature in association with PRES, however it is not clear whether autoimmunity drives PRES, whether immunosuppressive medications do, or whether a combination of these factors are responsible for PRES in the context of rheumatic disease [2, 6].

The list of differential diagnoses in PRES is long and includes top-of-the-basilar stroke, hypertensive encephalopathy, infectious, paraneoplastic and autoimmune encephalitis, malignancy and Reversible cerebral vasoconstriction syndrome [11, 12].

Removal of the precipitating trigger, prompt and aggressive management of blood pressure and antiseizure medications are empiric treatments commonly used in managing PRES. Many patients require ICU admission for close monitoring of neurological phenomena and cautious control and monitoring of blood pressure [11, 12].

The prognosis of PRES is variable. Whilst many cases are fully reversible within a period of days to weeks after removal of the inciting factor and control of the blood pressure, permanent neurologic disability and death are reported in the literature [6, 5].

Clinical and radiological features of PRES are summarised in Table 1. Whilst CT can be used to make the diagnosis, MRI is preferable.

Clinical Features
• Headache • Seizure • Altered conscious state • Visual disturbance
Features on MRI imaging
• Involvement of any of the occipital lobe, cerebellum and brain stem and less commonly the cervical spine and frontal lobes • White Matter oedema • Involvement of subcortical white matter • Confluent areas of increased signals on T2-weighted images • Distribution not confined to a single vascular territory • Fluid-attenuated inversion recovery (FLAIR) sequences increase sensitivity and are capable of detecting involvement of peripheral anatomy

Table 1: Clinicoradiological Features of Posterior Reversible Encephalopathic Syndrome [3, 5, 4].

Features that distinguish PRES from posterior cerebral infarctions, one of the major differential diagnoses, includes sparing of the grey matter and lack of involvement of calcarine and paramedian components of the occipital lobe. Diffusion-weighted imaging (DWI) can assist in in the differentiating PRES from top-of-the-basilar stroke [12].

The pathophysiology of PRES is thought to arise through a number of contributory mechanisms although the exact pathways remain to be elucidated. Current theories include the following four pathophysiological changes:

• Autoregulatory failure resulting in brain hyperperfusion, subsequent breakdown of blood brain barrier and extravasion of fluid and blood into brain parenchyma causing odemea [3]
• Cerebral ischemia potentially caused by one of the following:
o Dysregulation of local vasoconstriction and hypoperfusion
o Vasogenic oedema leading to compression of microcirculation and subsequent ischemia [6]
• Endothelial dysfunction resulting in extravasation of capillary fluid and subsequent oedema [5]
• Other mechanisms including metabolic and electrolyte disturbances including hypomagnesemia and fluid overload states [6]

2. Case

A Caucasian female in her early twenties presented to the authors' emergency department for severe right upper quadrant (RUQ) pain. The patient had known cholelithiasis and was on a waiting list for non-urgent elective cholecystectomy. The patient underwent investigations and imaging to rule out cholecystitis and remained in the emergency department for surgical review and management of ongoing RUQ pain. During this time the primary author became interested in the patient's past medical history and noted it had

features consistent with a possible HCTD.

2.1 Past Medical History:

Perinatal pneumothorax
Obesity grade III, BMI 40
Asthma
Dysfunctional Uterine Bleeding DUB and menorrhagia
Non-alcoholic fatty liver disease
Recurrent nephrolithiasis
Developmental delay with dyslexia
Chronic cognitive changes with memory impairment
Pulmonary embolism PE despite prophylactic enoxaparin post ureteric stenting
Subsequent multiple Pulmonary Emboli thought to be due to immobility
Postural Orthostatic Tachycardia Syndrome POTS (diagnosed by tilt table testing Dec 2020)
Ankle fracture
Multiple ankle sprains
Chronic lower back pain
Chronic widespread musculoskeletal pain
Sensory neuropathy secondary to multiple nutritional deficiencies
Reactive hypoglycaemia
Chronic RUQ pain and cholelithiasis
Depression
Obstructive Sleep Apnoea
Subclinical hyperthyroidism
Accidental opiate/paracetamol overdose
Recurrent PRES
Cortical Blindness

2.2 Past surgical history:

Nissen fundoplication age 2 years
Tonsillectomy 6 years old
Appendicectomy 9 years old
Ureteric stenting 2019
GI endoscopy 2019
Roux-en-Y gastric bypass procedure 2019

In 2019 the patient underwent a Roux-en-Y gastric bypass procedure for a high body mass index of 40. 10 days Post procedure she experienced a seizure, ataxia, hypertension and loss of vision, which was not reversible despite admission to the Intensive Care Unit (ICU) with management of hypertension and administration of antiseizure medications.

In 2021 the patient felt generally unwell and presented to the emergency department for assessment. The patient was noted to be slurring her words and unable to walk. She was hypotensive and hypoxic. Blood tests revealed liver function derangements and the patient developed multi-organ dysfunction. It was thought she might have suffered an accidental opiate and paracetamol overdose. The patient's GCS rapidly deteriorated and she was intubated, following which she experienced multiple seizures. The patient was retrieved by air to one of the major metropolitan hospitals where MRI brain imaging again confirmed a diagnosis of PRES. This resulted in permanent cortical blindness.

2.3 Family history:

Generalised joint hypermobility (GJH) in multiple family members including older sister and older brother who had been a competitive gymnast.

2.4 Regular medications:

Oxycodone
Pregabalin
Panadeine Forte
Pantoprazole
Ivabradine
Duloxetine
Fluticasone
Targin
Diazepam

2.5 Allergies:

Amoxicillin
Flucloxacillin
Ibuprofen

2.6 On Examination:

On examination, the findings suggestive of a connective tissue weakness included soft doughy pale skin through which blue veins were visible. The patient's skin was particularly hyperextensible on the patient's arms and neck. The backs of the patient's hands were less hyperextensible stretching to 1.5cm. Bilateral blue sclera were noted. The patient stated she had previously been able to touch the ground with her palms flat in the absence of knee flexion, however her current body habitus prevented her achieving this manoeuvre. The texture of the patient's muscles was hypotonic.

A flat papyraceous scar was noted on the patient's chest. There was no audible murmur on auscultation of her chest. Pale skin with visible blue veins were noted across the patient's chest and arms. The patient was noted to have keratosis pilaris on both arms and multiple striae over her arms and abdomen.

The patient did not have bifurcation of the uvula and did not have a Marfanoid habitus. She did not have epicanthal folds, subcutaneous spheroids, piezogenic papules, any current, or previous hernias. She did not have any muscle contractures, or chest wall deformities.

Generalised Joint Hypermobility was assessed using the Five-Part Questionnaire (5PQ) [13] as well as the Beighton Score [14]. The patient scored 4/9 on the Beighton Score for bilateral knee hyperextension, bilateral little finger hyperextension and answered

2 on the 5PQ for answering "yes" to the following questions: Can you now (or could you ever) place your hands flat on the floor without bending your knees? Do you consider yourself double-jointed?

No investigations, or imaging relating to a HCTD were performed at the time of presentation in ED. Imaging at the time the patient developed symptoms post-surgery in 2019 lead to a diagnosis of PRES were reported as follows:

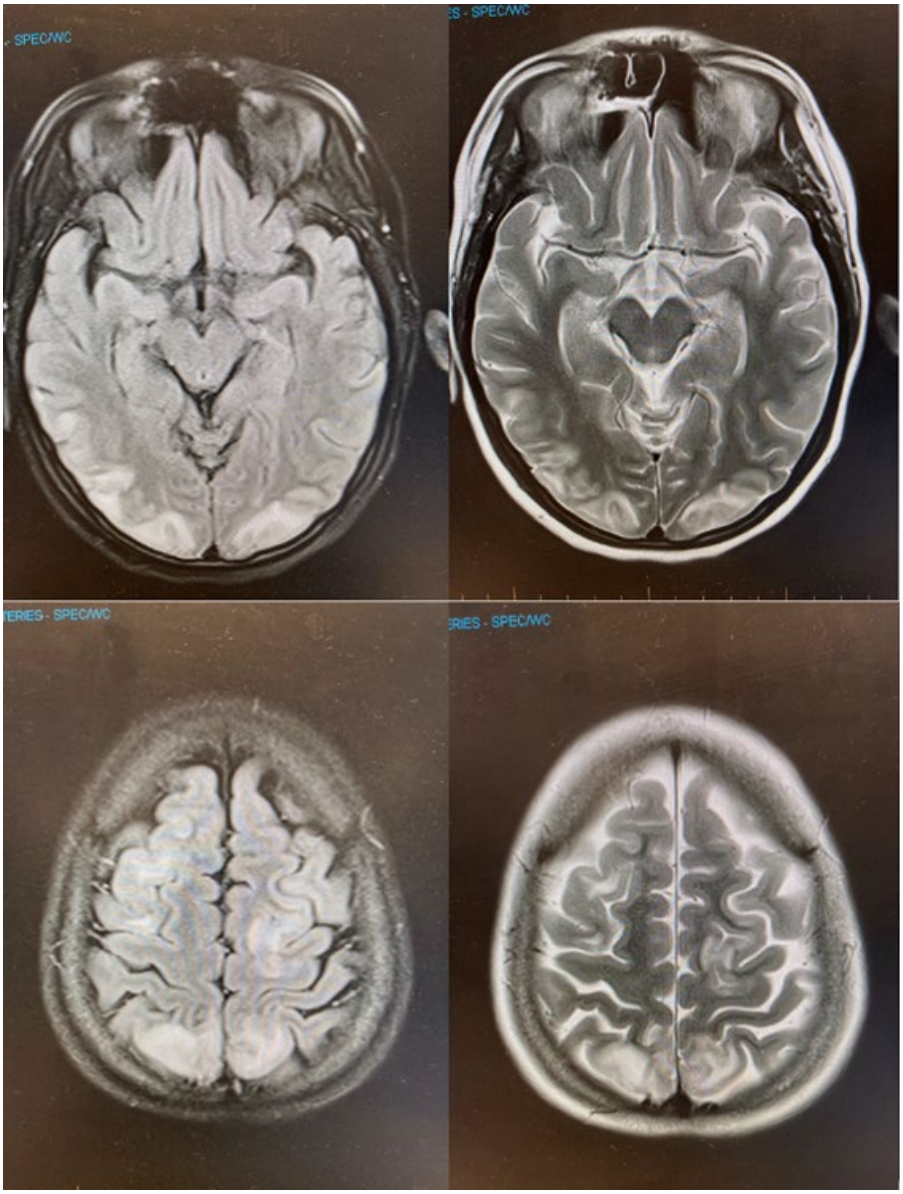
2.7 MRI Imaging Performed 10 Days Post-Roux-En-Y Gastric Bypass Surgery in 2019:

On flair imaging there is increased signal more apparent posteriorly in relation to subcortical white matter. This abnormality is also present with respect to superior subcortical white matter. DWI demonstrates corresponding areas of vasoconstriction. T2 imaging suggests the abnormality predominantly involves the subcortical with matter with preservation of the cortex. There are no features of haemorrhage. Ventricular dimensions are normal. MRA did not identify any vascular abnormality and there was no evidence of posterior circulation abnormalities including no artery wall irregularities, or areas of spasm. No abnormalities of the Circle of Willis were detected on FLAIR sequencing.

The images support a diagnosis of PRES.

At the time of diagnosis, the patient's subclinical hyperthyroidism was ruled out as contributing to PRES.

Image 2. DWI and T2 weighted imaging demonstrating findings suggestive of PRES



The second time the patient was diagnosed with PRES in late 2021 MRI imaging was reported as follows:

There is cortical thickening which is symmetrically in the bilateral occipital lobes, and to lesser extent in the right frontal lobe. The thickened cortices have high T2/FLAIR signal and diffusion restriction. No blooming artefact on the SWI sequence to suggest microhaemorrhage. There is prominent enhancement in the affected areas which is favoured to reflect increased vascularity with a differential of leptomeningeal enhancement. There is no evidence of papilloedema, or arachnoid outpouchings to suggest intracranial hypertension.

Given the anatomical distribution of these signal abnormalities the favoured differential diagnosis is PRES with a differential of a post-ictal state. Meningoencephalitis is felt less likely. The major intracranial vascular flow voids are preserved. The ventricular and sulcal calibre is stable and age appropriate. There is no midline shift or trans-compartmental herniation. There is high T2 signal seen in the mastoids compatible with moderate bilateral mastoid effusions. Mucosal thickening in the paranasal sinuses is compatible with sinus disease. The orbits are unremarkable.

The patient is intubated.

Symmetrical bilateral cortical thickening of the occipital lobes with abnormal signal is favoured to reflect PRES.

3. Discussion:

3.1 Differential Diagnosis

The 2017 classification criteria for Classical EDS according to [15], are shown in Table 2. For a patient to meet these criteria at least 1 major criterion and 3 minor criteria are required.

Major Criteria
1. Skin hyperextensibility and atrophic scarring 2. Generalized joint hypermobility (GJH)
Minor Criteria
1. Easy bruising 2. Soft, doughy skin 3. Skin fragility (or traumatic splitting) 4. Molluscoid pseudotumors 5. Subcutaneous spheroids 6. Hernia (or history thereof) 7. Epicanthal folds 8. Complications of joint hyper-mobility (e.g., sprains, luxation/ subluxation, pain, flexible flatfoot) 9. Family history of a first degree relative who meets clinical criteria

Table 2: Classification Criteria for Classical EDS (cEDS) [15].

The patient meets the clinical criteria for classical EDS due to the presence of both major criteria of Generalised Joint Hypermobility and skin hyperextensibility. The patient meets 4 of the minor criteria including soft doughy skin, skin fragility, easy bruising and complications of hypermobility including frequent ankle sprains and chronic musculoskeletal pain. A formal diagnosis requires genetic testing.

Additional features in the patient's examination and history suggestive of the presence of a HTCD/EDS include:

- Blue sclera
- Dysfunctional Uterine Bleeding with Menorrhagia
- Postural Orthostatic Tachycardia Syndrome
- Developmental delay
- Cognitive dysfunction
- Chronic widespread pain
- Hypotonia
- Family history of significant generalised joint hypermobility
- Pulmonary emboli

Keratosis pilaris has been reported to occur in association with EDS in a number of case reports [16, 17, 18] .

Combing the clinical findings, patient history and family history, the most likely differential diagnosis is Classical Ehlers Danlos Syndrome [19] followed by Hypermobile Ehlers Danlos Syndrome (H-EDS)[18]. Vascular Ehlers Danlos Syndrome is unlikely in the absence of a family history of sudden death and catastrophic rupture of hollow organs, or arterial dissection. The patient also has signs of generalised joint hypermobility (GJH) which is not a feature of Vascular EDS which usually involves peripheral hypermobility

of the digits. HANAC syndrome is a differential diagnosis given the patient's history of PRES, recurrent nephrolithiasis requiring stenting and muscle cramps, however cerebral angiography and other imaging the patient has previously undergone, including echocardiogram, has failed to identify any aneurysms.

Other disorders of the basement membrane relating to defects of collagen type IV are unlikely in this case due to absence of defining clinical features associated with such syndromes. These disorders include Thin Basement Membrane Disorder, Allport Syndrome, Goodpasture Syndrome and Nail Patella Syndrome.

Over 90% of patients with c-EDS are positive for a mutation in Col5A1, or Col5A2 genes, those that encode for type V collagen. Rarely mutations in genes encoding for type I Collagen have reportedly given rise to c-EDS [15].

Genetic testing in combination with referral to a rheumatologist is crucial in making a diagnosis in this type of presentation. Genetic tests exist for classical and vascular EDS, but not for hypermobile EDS which relies on clinical criteria as outlined by [15]and [19].

At the time of writing this paper the patient had not undergone genetic testing and remained on the waiting list for assessment by genetic services, which is a long waiting list of over 10 months due to a limited resources within the public health system and an absence of private services.

3.2 Possible Contributing Factors to the development of PRES in the Context of HCTDs

3.2.1 The Autonomic Nervous System

Cerebral autoregulation is the ability of the brain to maintain stable intracerebral blood flow, despite changes in systemic blood pressure [20]. Central to this is activity regulated by the autonomic nervous system [4] Dysregulation of cerebral blood pressure has been cited as a contributory factor in development of PRES [10] and is known to contribute to cerebral ischemia which is one of the mechanisms thought to play a role in PRES pathophysiology.

Whilst hypertension and cerebral hyperperfusion is recognised in PRES, about 30% of patients have normal, or low blood pressure [4]. These discrepancies in case reports have resulted in controversy around theories surrounding cerebral hypertension and its contributory role in PRES [3]. Dysregulation of systemic blood pressure as well as cerebral blood pressure due to dysautonomia is one possible explanation for reported differences in systemic blood pressure in patients who develop PRES. Therefore, there is the possibility that comorbidities such as Postural Orthostatic Tachycardia Syndrome (POTS) and EDS as well as other rheumatic diseases where autonomic dysregulation exist could potentially contribute to the pathogenesis of PRES.

Dysautonomia is a clinical feature occurring very frequently in rheumatic disease [21] in between 24% to 100% of patients (Stovanovish).

Cerebral hypoperfusion has been noted in some PRES cases [22]. Reduced cerebral blood flow and loss of autoregulation of cerebral blood pressure is reported in POTS with associated difficulty adjusting to rapid fluctuations in systemic blood pressure [23, 24, 25]. There is a close association between POTS, EDS and HSD 30% of patients with POTS meet classification criteria for hEDS [26]. The presence of POTS should always prompt screening for EDS and HSD especially in young female patients. POTS has not previously been reported in association with PRES, however numerous case reports recognise PRES can be triggered by dysautonomia in association with other conditions, mainly Guillain-Barre Syndrome [27, 28, 29]. This is an area that requires further research as GJH and connective tissue disease are frequently missed comorbitidies in these patient cohorts and there is a recognised relationship between EDS rheumatic diseases and other autoimmune disorders (Rogers).

3.2.2 Connective Tissue in the Brain's Extra-Cellular Matrix (ECM) and the Blood Brain Barrier

Our understanding of connective tissue components of brain parenchyma is still evolving. In vivo studies prove challenging. Increasingly research is being directed towards the role of the connective tissue within the ECM in various pathological processes of the Central Nervous System (CNS) [30]. Collagen and collagen producing cells are found not only in the meninges and along the brain's blood vessels, but have also been reported within neural parenchyma of the brain. Collagen type I, III, IV, VI and XVII are all found throughout various anatomical sites of the brain [31].

Astrocytes that form part of the blood brain barrier secrete glycoproteins and proteoglycans that affect immunologic responses and might be responsible for a range of pathophysiological processes [32].

TGFβ1 exposure has been shown to cause pericytes surrounding the BBB to secrete abnormal collagen I, III and IV in the context of hypertension, leading to BBB leakage [33]. This process is linked to the development of vascular dementia [33]. The role of other subtypes of collagen and components of the ECM in the brain is yet to be fully understood. Patients with HCTD affecting collagen I (c-EDS), III (VEDS) and other collagen subtypes might have altered BBB pericyte function affecting a range of pathophysiological processes leading to the development of PRES.

The architecture of blood brain barrier is a specialised membrane created by a number of cells including astrocyte end feet, brain microvascular endothelial cells and pericytes that are embedded within the connective tissue of the basement membrane [34]. In the BBB there are 2 types of basement membrane [34]. The first basement membrane is the endothelial basement membrane

comprised of laminin, fibronectin, collagen type IV (of which there are six isomers), nidogen and perlecan [34]. The second basement membrane is the perivascular glia limitans formed by fibronectin, agrin and laminans [34].

Tight junctions which form a central role in BBB function are constructed from a number of proteins including ZO-1, 2,3 occludins and claudins [34]. This structure as a whole can be considered as an organ called the neurovascular unit (NVU) [34].

Disruption of the tight junctions of the blood brain barrier resulting in extravasion of blood and fluid is a component of the pathophysiology in PRES [4]. Therefore, it is possible that conditions resulting in weakness of the blood brain barrier (BBB) could possibly lead to leakage with subsequent oedema precipitating PRES.

In HANAC syndrome the reported neurological features could be due to dysfunction of the blood brain barrier which is known to contain collagen type IV [35]. Since HANAC syndrome involves a mutation of collagen IV gene this would possibly explain the development of PRES in this condition. Other disorders affecting collagen IV such as Alport Syndrome, or Goodpasture Disease could result in PRES. There are case reports of Alport Syndrome and Goodpasture Disease and development of [36, 37] .

The extra cellular matrix (ECM) plays a central role in the integrity and function of connective tissue [19]. Defects in the extracellular matrix including the phenomenon of anoikis [38] have been reported as contributing factors in EDS and other HCTDs [19], particularly in classical EDS and vascular EDS. Defects in the proteins of the ECM could potentially cause disruption of normal extra cellular matrix function with subsequent disruption of the BBB. However, this is an area that has not previously been studied to be best of the author's knowledge.

Autoregulation of cerebral blood blow is maintained through the release of vasoactive substances including endothelin-1, Nitrous Oxide (NO) as well as carbon dioxide. Endothelial dysfunction has been noted to occur in several rheumatic diseases and is thought to play a role in the development of PRES. Endothelial dysfunction is reported in Vascular EDS patients with possible aberrant NO manufacture [39]. It is plausible that endothelial dysfunction exists in other EDS subtypes and plays a role in reported autonomic dysfunction, however this represents a gap in current EDS research.

Altered fibroblast activity is also noted in classical, vascular and hypermobile EDS [40]. Fibroblasts play a role in repair of the blood brain barrier and might contribute to the clinical features of PRES following the initial development of the condition.

Aberrant genes responsible for Collagen I, II, IV and other collagen subtypes as well as other components of the ECM both within the BBB architecture, or in the brain parenchyma could predispose patients with HCTDs to development of PRES.

Aberrations in chemistry regulating functional components of the BBB might play a role in development of PRES. This includes a host of oxidative species, vitamins and inflammatory molecules as well as possible genetic mutations involving AQP4, SOD1 an APOE and even microbiota activity within the gut-brain axis which are all integral components of a healthy functioning BBB Dysregulation of the complex homeostatic symphony of chemical pathways, immune response, microbiota and other factors discussed here might play a role in BBB dysfunction and the development of PRES. Even subtle disruptions to the function of a healthy BBB are known to produce significant pathophysiology in certain instances (Rustenhoven). Patients with pre-existing immunological dysfunction, or who are taking immunosuppressive and cytotoxic medications might therefore be vulnerable to BBB dysfunction and this could be a possible mechanism in leakage, subsequent oedema and development of PRES. This is a complex area that represents a gap in current understanding of PRES pathophysiology.

Whilst no case studies linking EDS with the development of PRES exist there are 4 case studies where spontaneous carotid artery dissection have been reported to trigger the condition [41], with 3 of these being connected to a post-partum state [42]. These case studies possibly represent missed EDS/HSD, or other HCTD diagnoses as pregnancy can exacerbate connective tissue disease weakness due to altered endocrine function including increased relaxin synthesis [43].

In line with the Fugate and Rabenstein Algorithm [3] and discussion by Faille [5], the authors recommend patients with known HCTDs, or autoimmune-driven rheumatic disease who present with neurological episodes such as new onset seizure activity, encephalopathy, confusion and who have other risk factors such as renal impairment, fluctuating blood pressure especially hypertension, are on immunosuppressive or cytotoxic medications, or who develop eclampsia, PRES should be considered in the differential diagnosis as this will lead to improved knowledge of incidence of PRES in these patient groups.

• A high degree of clinical suspicion for EDS or other HCTDs must exist in young patients who present with POTS, multiple complex medical conditions and clinical features suggestive of possible connective tissue weakness • A number of mechanisms in disorders of connective tissue weakness might contribute to loss of autoregulation and brain hyperperfusion, or hypoperfusion, endothelial dysregulation and brain oedema from dysfunction of the blood brain barrier resulting in PRES • There is a paucity of research on the relationship between HCTDs, PRES and BBB dysfunction • Further research to establish whether there is a connection between POTS, autonomic dysfunction, EDS/HSD is required as the presence of these conditions might be underdiagnosed in patients presenting with PRES • In patients with autoimmune rheumatic diseases and HCTDs as per the Fugate and Rabenstein (2010) algorithm patients who present with fluctuating blood pressure and a neurological episode such as seizure, sudden visual disturbance, or confusion should be screened for PRES • Opportunistic screening of patients for GJH in the emergency department can prevent missed diagnosis of HCTDs • Patients who develop PRES are likely to be either hospital in-patients, or present to emergency departments for assessment, therefore education of emergency department doctors to facilitate recognition of PRES and HCTDs is required

Table 3: Key Learning Points

4 Conclusion

This case study represents a possible association between a likely heritable disorder of connective tissue HCTD and the development of Posterior Reversible Encephalopathic Syndrome PRES. Several mechanisms are proposed that would account for this relationship including weakness in the blood brain barrier and autonomic dysregulation leading to aberrant intracerebral blood pressure and blood blow [44-58].

The authors note that features of possible connective tissue weakness in patients' history are subtle, complex and might be overlooked, but improved awareness of associations between comorbidities such as POTS, uncommon surgical complications and various clinical signs which are easy to assess in an Emergency Department context should trigger screening for HCTDs in particular EDS/HSD.

Conflict of Interests:

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Patient Consent:

The authors obtained patient consent for use of imaging and patient information and approval from the hospital CEO for the authoring and publication of this paper.

Contributors:

The primary author contributed to the conception and design of the work, drafted the manuscript and conducted the literature review. The secondary author revised the paper for important intellectual content and critical evaluation. Both authors give final approval of the version to be published and agreed to be accountable for all aspects of the work.

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