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TITLE: Psychiatric morbidity and its prognosis in posterior reversible encephalopathy syndrome (PRES)

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ABSTRACT

Posterior reversible encephalopathy syndrome (PRES) is a clinically and radiologically-diagnosed disorder characterised by subcortical vasogenic cerebral oedema. To date, its presentation has been described through summarised neurological categories, such as seizures, headaches, 'confusion' and 'altered mental function'.

This retrospective case series identified all clinically-confirmed, radiologically-diagnosed PRES cases treated in a large teaching hospital from 2010-2019. The hospital clinical radiology information system was searched for "reversible encephalopathy", after which scan reports and clinical records were audited. The study was authorised by South London and Maudsley NHS Foundation Trust's Clinical Audit and Effectiveness Team.

Forty-seven confirmed cases were identified. Seizures (81%) and reduced consciousness (62%) were the commonest presentations. Radiological abnormalities were most commonly bilateral (94%), asymmetrical (57%) and affected occipital (85%), parietal (79%), frontal (43%), temporal (36%) and cerebellar (26%) regions. Acute hypertension (72%; mean blood pressure 185/109 mmHg) and drug toxicity (57%) were common suspected precipitants (30% tacrolimus, 22% ciclosporin); sepsis occurred in 47% of cases. A sub-group (38%) had contact with psychiatric services (out of all 47 cases, 15% premorbid, 21% during PRES admission, 21% post-discharge). They were more often female (83 vs. 70%) and somewhat older (median age: 44 vs. 39 years), with higher total mortality (33 vs. 28%). Commonest reasons for psychiatric referral were addictions, acute psychosis, depression, suicidality and refusing treatment.

Multidisciplinary staff should consider PRES as a rare organic differential diagnosis for acute mental state changes. Physicians treating PRES should be aware of elevated rates of post-PRES psychiatric symptoms and consider whether psychiatric input would enhance recovery.

TEXT

Introduction

Posterior reversible encephalopathy syndrome (PRES) is clinically and radiologically-diagnosed, characterised by subcortical vasogenic cerebral oedema, with characteristic neuroimaging appearances. Its commonest known precipitants are drug toxicity,{1} hypertension, sepsis,{2} pre-eclampsia and auto-immune disease. A review of 20 years' literature highlighted unanswered questions about PRES' underlying pathophysiology, diagnostic criteria and prognosis.{3} The importance of clinical suspicion has been emphasised{4} but presenting symptom descriptions have been confined to summarised neurological categories, such as seizures, headaches, 'confusion' and 'altered mental function'.{5-7} Studies of the psychiatric sequelae of PRES and its mental health comorbidity are absent from the literature.

Following the description of new neuropsychiatric syndromes such as anti-NMDA receptor encephalitis,{8} interest in potentially reversible 'organic' aetiologies of psychiatric presentations has expanded markedly.{9,10} Research on psychiatric outcomes of acute neurological disorders is well-established but recent work on encephalitides is noteworthy, reporting high rates of anger, anxiety, mood swings and low mood.{11} For example, a large, population-based retrospective cohort study found elevated risk ratios (RR) for bipolar affective disorder (RR=6.34), psychotic (3.48), depressive (1.88) and anxiety disorders (1.46) post-encephalitis.{12} Comorbid psychiatric disorders are associated with worse quality of life in a range of neurological disorders, including multiple sclerosis {x}, epilepsy {y} and migraine {z}.

Based on clinical experience, we hypothesised that a proportion of patients diagnosed with PRES develop psychiatric symptoms during and after the acute illness. We sought to identify all cases of radiologically-diagnosed PRES in a large teaching hospital over a nine-year period, to audit psychiatric precipitants, symptoms and sequelae, alongside clinical and aetiological correlates.

Methods

We report a retrospective case series conducted in the liaison neuropsychiatry service of a large south London teaching hospital serving four south London boroughs, of PRES cases presenting between April 2010 and April 2019. The study was authorised by South London and Maudsley NHS Foundation Trust's Clinical Audit and Effectiveness Team on 16/06/2016. We retrieved records from the hospital's clinical radiology information system using the search term "reversible encephalopathy" to address disambiguation problems with "PRES". For each patient where a scan report mentioned "reversible encephalopathy", we reviewed clinical and radiological records to determine whether PRES was ultimately the confirmed diagnosis. We audited those cases' clinical records using a piloted data collection form and entered pseudonymised data into a spreadsheet stored in password-protected hard drives.

Results

Case detection

Of an initial 123 results, 69 were excluded at initial screening, as duplicates (n=18), not having a scan recorded (n=13) or PRES being ruled-out radiologically (n=38); see Figure 1. Of 53 clinical notes reviewed, we excluded seven where the ultimate clinical or radiological impression was not PRES. Forty-seven were included in the final sample, including one which was reported by the neurology team.

Demographics

Of 47 included cases, 33 (70%) were female, with median age 39 years at presentation (range: 5-74 years).

Neuroimaging

Radiological reports indicated that abnormalities were bilateral in 44 (94%) cases, of which 25 (57%) were asymmetrical. Grey matter involvement was mentioned in 23 (49%) reports and abnormalities were more pronounced in posterior than anterior regions in 40 (85%). Involved brain regions were occipital (40 cases; 85%), parietal (37; 79%), frontal (20; 43%), temporal (17; 36%), cerebellar (12; 26%), basal ganglia (7; 15%) and brainstem (4; 9%).

Presenting symptoms

The commonest presenting symptoms were seizures (38; 81%), reduced consciousness (29; 62%), headache (12; 26%), visual abnormalities (26%), nausea and vomiting (11; 23%). Focal neurological signs were documented in 10 (21%) cases, confusion and agitation in seven (15%) cases each.

Aetiology

Acute hypertension was identified in 34 (72%) cases. Where blood pressure at the time of presenting symptoms was electronically documented, the mean systolic pressure (n=22) was 185 mmHg (range: 140-220) and diastolic pressure (n=17) was 109 mmHg (range: 71-140). Possible drug toxicity was identified in 27 (57%) cases, comprising tacrolimus (8; 30%), ciclosporin (6; 22%) and a range of other agents (1-2 cases each), including cancer chemotherapeutic agents, anti-inflammatory drugs and antibiotics. Infection or sepsis was present in 22 (47%) cases, of which 10 (46%) were chest sepsis, three (14%) each were HIV opportunistic infections and skin infections, and a range of others including clostridium difficile diarrhoea (two cases).

Medical comorbidities

The commonest medical comorbidities were haematological (14; 30%), including aplastic anaemia (n=3), acute leukaemias (3), myelodysplastic syndrome (2) and sickle cell anaemia (2). The second commonest comorbidities were auto-immune disorders (13; 28%), including systemic lupus

erythematosus (5; 38%), sarcoidosis (2; 15%) and autoimmune hepatitis (15%). Chronic liver disease affected 11 (23%) cases and chronic kidney disease 8; (17%), of which 88% required renal replacement therapy. Seven cases were diagnosed with malignancy (15%), four had a history of seizures (9%) and three (6%) cases occurred in pregnancy or post-partum.

Management

The commonest treatments were antiepileptic medication (13 cases; 27%), antihypertensive medication (27%), or a combination (8; 17%). Five cases (11%) received treatment for potential central nervous system infection and in 11% no specific treatment for PRES was provided beyond management of comorbid disorders or withdrawal of the suspected toxic agent.

Prognosis

Seven cases (15%) died during the index hospital admission, one was discharged to palliative care and five died since, a mortality rate of 28% during the follow-up period. Age of death ranged from five to 74 years, with a median of 41 years.

Psychiatric contact

Eighteen (38%) cases had some form of contact with local psychiatric services. This sub-group had a higher median age (44 years), proportion of females (83%) and mortality rate (33%) than the full sample. Psychiatric service contact comprised pre-PRES input (n=7: 15% of all cases), liaison psychiatry referrals during the index admission (21%) and post-PRES input (21%). Median duration of psychiatric service input from PRES onset until discharge was 677 days (range: seven to 3123 days).

Premorbid

Reasons for psychiatric treatment prior to PRES comprised assessments of low mood and suicidality (29%), regular input from addictions services (29%), mental capacity assessments when refusing dialysis (29%) and routine assessment pre-transplant (14%).

Psychiatric PRES symptoms

Twelve PRES case records (26%) documented mental state abnormalities. These comprised speech disturbance (67%), confusion (58%), agitation (58%), hallucinations (33%), disinhibition (25%), low mood (25%), delusions (17%), bad or vivid dreams (17%), religious preoccupation, self-harm and anxiety (all 8%). Of the 10 cases referred to liaison psychiatry, only one was reviewed for symptoms directly related to PRES and three for symptoms identified once PRES had been treated. The remaining referrals were for an overdose that precipitated the admission (20%), cognitive or mental capacity assessment (20%) or substance use nurse review (20%). The case referred during PRES was reviewed for grandiose and persecutory delusions and auditory hallucinations. The three cases assessed for post-PRES symptoms were referred for (i) agitated depression and suicidality, (ii) low mood and vivid dreams and (iii) advice about antipsychotic medication.

Psychiatric symptoms post-PRES admission

Of the 10 cases receiving psychiatric services post-PRES admission, four were referred for low mood, alongside acute delusions, suicidality, erratic behaviour or reduced oral intake. Four were referred regarding capacity to refuse treatment or self-discharge; in three of these, comorbid addictions were present. Two cases were referred with acute confusion, alongside persecutory delusions or rapid cognitive decline.

Discussion

Psychiatric symptoms were not reported in all PRES cases, although confusion and agitation were common. However, psychiatric symptoms often arose before, during or following PRES, in keeping with evidence of psychiatric comorbidities in neurological disorders including epilepsy, migraine, stroke and traumatic brain injury.{13} The psychiatric sub-group was a median five years older, with a higher proportion of females than the full sample and a higher mortality rate (33% vs 28%).

Physicians treating PRES and liaison psychiatrists must be alert to this comorbidity. Multidisciplinary staff should consider PRES a rare organic differential diagnosis for acute mental state changes, especially alongside neurological signs, hypertension or medical comorbidities. Physicians treating PRES should assess for post-PRES psychiatric symptoms, considering whether liaison, specialist substance use or community psychiatric follow-up could enhance recovery.

Given these rates of psychiatric comorbidity, it is striking that the subject is near-absent from PRES literature, which focuses on neuroimaging, neurological sequelae, treatment and prognosis. This is surprising, given the association between neuropsychiatric symptoms and temporo-limbic network lesions, which are not uncommon in PRES. Despite the term 'reversible,' residual infarcts and subsequent leukomalacia are recognised sequelae of PRES,{14} supporting the likelihood of longer-term psychiatric symptoms in a proportion of patients, as is well-recognised for acute neurological disorders such as encephalitis.{11,12}

As expected, this sample had high rates of underlying medical comorbidity. Worldwide, depression prevalence is higher in people with chronic,{15} including neurological,{16} disorders. In our sample, the commonest reasons for referral were alcohol and intravenous drug addictions, acute psychosis, depression, suicidality and refusing medical treatment due to delirium or agitation. There were few or no referrals for severe anxiety, longstanding psychotic illnesses, bipolar illness, intellectual

disability, personality or eating disorders. Perhaps during critical illness treatment and follow-up, only markedly acute psychiatric symptoms were detected by physicians and referred for assessment. It is not possible to say with certainty the extent to which some psychiatric morbidity pre-dating PRES may have gone undetected. Such morbidity would be expected to be increased over the population baseline in the context of chronic medical illness. The UK National Health Service system provides open access to family practitioners so most moderate to severe mental disorder is recorded. Substance misuse and dependence may however escape the attention of healthcare services.

This first study of its kind provides preliminary support for our clinically-informed hypothesis of elevated psychiatric morbidity in individuals following PRES, which requires more widespread, prospective investigation. A strength of our study is its relatively large sample size, drawn from a broad, diverse, densely-populated region of south-East London, in a teaching hospital with expertise in a range of relevant medical disorders. A limitation is its pragmatic, retrospective audit design, dependent on routinely documented free-text clinical records. Future research and PRES case series should investigate psychiatric comorbidity and sequelae systematically, including the premorbid period, to elaborate on these findings. Perspectives of patients and their carers on individuals' pre- and post-PRES mental states and longitudinal follow-up of neuropsychiatric outcomes would be particularly informative.

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Figure 1: Case detection flow diagram