REVIEW / REVUE DE LA LITTÉRATURE

REVERSIBLE SYNDROME OF EXTRAPYRAMIDAL MOVEMENT DISORDERS WITH BILATERAL BASAL GANGLIA LESIONS IN UREMIA: A CASE SERIES AND REVIEW OF THE LITERATURE

SYNDROME EXTRAPYRAMIDAL REVERSIBLE AVEC LESIONS BILATERALES DES NOYAUX GRIS CENTRAUX A L'IRM CAUSE PAR UNE HYPERUREMIE

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ABSTRACT

Background
The distinct clinicoradiological syndrome of reversible basal ganglia lesions associated with extrapyramidal movement disorders in uremic patients has rarely been described in the literature. There have been no reported cases from Africa.

Methods
This study is a retrospective analysis of uremic patients presenting with extrapyramidal movement disorders in Durban, South Africa from 2003 to 2016. A review of all published studies was also undertaken.

Results
Seven patients who presented with this syndrome were identified. An additional 41 cases were reported in the literature. Our seven cases showed similar characteristics to those previously reported. All patients were of Asian ethnicity and had dialysis dependent renal failure, 86% (6/7) due to diabetic nephropathy. The most frequent presentation was parkinsonism (5/7) followed by chorea (1/7) and dystonia (1/7). Typical neuroimaging findings included bilateral symmetrical basal ganglia abnormalities that were hypodense on computed tomography scan, and T1 hypointense and T2 hyperintense on magnetic resonance imaging. A key feature of this syndrome is its reversibility with supportive treatment; Clinical improvement was observed in 86% (6/7), which was accompanied by radiological regression of lesions in two patients who underwent follow-up imaging.

Conclusions
The syndrome of acute extrapyramidal movement disorders in uremic patients with bilateral basal ganglia lesions presents with typical clinical and radiological findings. Awareness of this syndrome especially in Asian diabetic patients with renal failure is important for early recognition and appropriate supportive management to aid its resolution.

INTRODUCTION

The clinicoradiological findings of the reversible basal ganglia lesions associated with Extrapyramidal Movement disorders in Uremia Syndrome (from here on referred to as "REMUS") has been described in the literature [11, 16, 18]. Characteristic features of this syndrome include the abrupt onset of symptoms, the presence of bilateral symmetrical basal ganglia lesions on neuroimaging as well as clinical and radiological reversibility with supportive management.

In a review article in 2008, Li et al. [11] summarised 24 cases of this syndrome published since its first description in 1998. Thereafter, only case reports and small case series have been documented. The true incidence in different populations has not yet been established but the majority of reports are of Asian patients. There have been no cases published from Africa [11, 17].

REMUS is distinct from uremic encephalopathy, the more frequent central nervous system complication of renal failure. Uremic encephalopathy is characterised by cortical involvement presenting with seizures, impaired level of consciousness, asterixis and myoclonus. Clinically, the syndrome we describe affects the basal ganglia and therefore manifests with hyperkinetic or hypokinetic movement disorders. Patients may have disturbances in consciousness, but this is usually mild and not the predominant feature [17].

Considering that knowledge of REMUS is based on limited case reports and one previous review article published a decade ago [11], an updated description of the syndrome will be advantageous to enhance recognition and optimal management. In this study, we report our experience of patients with REMUS in an African setting. In addition, we summarised published data of all previously reported cases and compared these to our series.

METHODS

A retrospective chart review was performed on patients who presented in renal failure with movement disorders and bilateral basal ganglia lesions from 2003 through 2016 in Durban, South Africa. The biomedical research ethics committee (BREC) of University of Kwa Zulu Natal (UKZN) approved the study (BE 038/17).

In addition, we performed a literature search to identify all cases published since the first description of this syndrome in 1998 until August 2017. Search engines and electronic databases included Pubmed, Google scholar, Science Direct, Biomed Central and UKZN World Cat. English language articles reporting patients who met the following clinical criteria were included: uremia (serum urea more than 7.1mmol/l), hypokinetic or hyperkinetic movement disorders and bilateral basal ganglia lesions on neuroimaging studies. Cases were excluded if neurological dysfunction was reported in the absence of movement disorders and if other possible causes of basal ganglia lesions were identified.

Data on the following parameters were extracted for all cases: ethnicity, age, gender, aetiology of renal failure, current dialysis and duration thereof, duration of symptoms, type of movement disorder, level of consciousness, laboratory and imaging findings, interventions provided and clinical and radiological outcomes. The country in which the cases were identified was also documented.

STATISTICAL ANALYSIS

Statistical analysis was performed using GraphPad Prism version 6. Continuous and categorical variables are presented as median and interquartile ranges and, percentages, respectively. Categorical and continuous variables between groups were compared using Fisher's exact test and, Mann-Whitney U test, respectively. A p-value of <0.05 was considered statistically significant.

RESULTS

We included seven cases presenting with REMUS. Details of these seven patients are summarised in Table 1. Amongst them, four (57%) were female. All patients were of Indian ethnicity. The median age was 52 years (range: 34-65years). Six patients (86%) had diabetic nephropathy as a cause for renal failure and one had hypertensive nephropathy. All patients were receiving chronic renal replacement therapy; two (29%) received peritoneal dialysis and five (71%) received haemodialysis for a duration of 18 months (median, range:12-24 months). Patients presented after a median of 21 days (range: 8-75) symptom duration with one patient reported as having "acute symptom onset" without the number of days of symptoms specified. Five (71%) patients presented with parkinsonism, one (14%) with chorea and one (14%) with dystonia. Three (43%) patients had impaired level of consciousness. The median urea was 14 mmol/l (range: 13-18) and creatinine 844 umol/l (range: 754-918, in six patients for whom this result was available). Two (40%) of five patients were acidotic.

Neuroimaging performed included computed tomography (CT) in two patients (29%) and magnetic resonance imaging (MRI) in six (86%). CT scans showed bilateral basal ganglia hypodensities (Figure 1). The MRI universally showed bilateral symmetrical basal ganglia signal changes that were hypointense on T1 weighted images hyperintense on T2 weighted images (Figure 2). One patient demonstrated extension of these abnormalities into the posterior parietal regions and another patient had involvement of the internal and

external capsules as well as the medial temporal lobes. Of those who had MRI, two showed evidence of vasogenic and cytotoxic oedema on diffusion weighted imaging (DWI) and apparent diffusion coefficient (ADC) imaging. All patients were dialysed. Medical therapy included levodopa in the five patients with parkinsonism, haloperidol in the patient with chorea and, a combination of risperidone and clonazepam in the patient with dystonia. Two patients (29%) showed complete clinical recovery and an additional four (57%) showed clinical improvement. One patient died shortly after admission due to severe uremia and concurrent infection. Two patients who underwent follow-up imaging showed radiological improvement.

The literature search identified 38 articles. Seven case reports were excluded due to absence of movement disorders and three case reports and one case series (2 patients) were excluded due to the possibility of an alternative/additional etiological cause for basal ganglia lesions (e.g. hypoglycaemia, thiamine deficiency and drug effects). From the 27 articles included, 41 cases were described. Details of these patients and a comparison to our case series are provided in Table 1. No statistically significant results were obtained when comparing our case series to the previously published cases.

DISCUSSION

REMUS is a rare disorder, most commonly reported from Asia. In this first case series from Africa, we describe seven patients with end stage renal failure on chronic renal replacement therapy with this syndrome. Six patients showed improvement after dialysis and pharmacotherapy. Our patients showed similar characteristics to the 41 cases reported in the literature.

Patient demographics

Including our series, 79% of all cases thus far described in the literature were Asian, as all South African patients were of Indian ethnicity. Only three Caucasian and three Hispanic cases have been reported from Europe, America and Australia [2, 3, 6, 8, 11, 19] and there have been no reports of cases with African ethnicity. This may imply under recognition in these populations or an underlying protective genetic trait.

Renal failure

The most common setting of the syndrome is in patients with diabetic nephropathy and long standing renal impairment receiving chronic dialysis. Other causes of renal failure that have rarely been associated with REMUS include Polycystic Kidney Disease and Chronic Glomerulonephritis [6, 10]. No distinct additional precipitants of the syndrome were reported.

Clinical Presentation

This syndrome frequently has an acute or subacute presentation, however longer durations of up to 180 days have been documented [1]. As reflected in Table 1, parkinsonism is the most common clinical presentation, followed by chorea, then dystonia. A single case reported by Sheu et al.[13], demonstrated a relapsing remitting course, with episodes of altered sensorium and dyskinesia followed by parkinsonism, however the remaining cases, including those in our series, all had a monophasic disease course. We report acidosis in a smaller proportion of patients than previously described [11] (62% vs 90%).

Neuroimaging findings

A unique characteristic of REMUS is the uniformity of radiological findings amongst various cases, particularly the consistent symmetry of basal ganglia abnormalities. Lesions are hypodense on CT scans and MRI findings show basal ganglia T1 weighted hypointensities with corresponding T2 weighted hyperintensities. The extent of the signal changes ranges from focal involvement of the putamen or pallidum to the entire basal ganglia. The abnormalities are most commonly isolated to the basal ganglia, but have also been reported to extend into the thalamus and adjacent white matter [2, 4, 16]. Gadolinium and iodine contrast is rarely administered in patients with renal impairment, however in the eight patients who did have contrasted scans, basal ganglia enhancement was observed in two (25%) [9, 17]. Vasogenic oedema in the basal ganglia was observed on DWI in 95% (19/20) of cases. However, reduced ADC values suggestive of cytotoxic oedema were only demonstrated in 63% (12/19) of cases, most commonly affecting the central portions of the affected basal ganglia regions. Occasionally the presence of petechial haemorrhages within the basal ganglia lesions have also been reported [13, 17, 20].

Pathogenesis

The precise pathogenesis of the basal ganglia abnormalities in this setting remains unclear, but is likely to be multifactorial, due to a combination of diabetes, renal failure, toxins and metabolic derangements. Diabetes-associated microvascular changes in the basal ganglia may render it susceptible to damage. The acute onset and spontaneous improvement suggests ischemia as a possible pathogenic mechanism [11, 17, 18]. However, post-mortem analysis performed 10 months after syndrome presentation in a single patient did not show inflammatory changes or blood vessel damage in the basal ganglia [14]. This may suggest that microvascular disease is not a major contributing factor.

Magnetic resonance spectroscopy (MRS) imaging in one case showed findings suggestive of ischemia and glucose utilization failure [3]. This was supported by F-18 fluorodeoxyglucose (FDG) positron emission

tomography (PET) scans in two patients performed by Wang et al. [18], which revealed markedly reduced glucose metabolism in the basal ganglia, especially in the putamen where glucose uptake was almost absent.

The vulnerability of the basal ganglia to numerous toxins and metabolic disturbances is widely accepted [7]. One of the key features of REMUS is the presence of uremia and therefore uremic toxins have been implicated in the underlying pathogenesis. At present, no specific toxin has been shown to have a direct causative link but potential candidates include asymmetric dimethylarginine (ADMA), methylguanidine, parathyroid hormone and aluminium [11, 17]. Metabolic acidosis may also contribute to the pathogenesis as similar lesions have been described in patients with normal renal function but with metabolic acidosis due to other causes, such as methanol intoxication [7, 12].

Combining the above theories, Wang et al. [17] proposed the underlying pathophysiology as follows: Patients with longstanding diabetes already have sub-optimal basal ganglia function and reserve due to cerebral micro-angiopathic changes and impaired energy utilization. When exposed to uremic toxins, function decompensates leading to tissue damage and focal oedema manifesting clinically as movement disorders in the acute phase. As the oedema resolves, clinical and radiological improvement is seen, however cellular metabolic derangement may persist which explains why a small proportion of patients demonstrate poor recovery [18].

Management and outcomes

The most significant feature of the syndrome is the spontaneous improvement or even complete resolution, both clinically and radiologically, which distinguishes it from most of the other causes of basal ganglia abnormalities such as carbon monoxide, hypoxia and other metabolic disorders [11, 15]. Management is focussed on supportive care particularly intensifying dialysis to treat the acidosis and uremia. In addition, symptomatic treatment, including levodopa and benserazide for parkinsonism and, dopamine antagonists and benzodiazepines for hyperkinetic movement disorders, have also been administered in 31% (11/36) cases. However, the contribution of these agents to recovery is uncertain. PET scans using (11 C)-labeled 2-carbomethoxy-3-(4-fluorophenyl) trophane and (11 C)-labeled raclopride described by Ishii et al. [5], revealed significant decreases in pre- and postsynaptic dopaminergic neuron function in the basal ganglia bilaterally, suggesting that levodopa may not be effective in the treatment of parkinsonism in these patients [5]. Overall, good clinical outcome was seen in 79% of cases whilst radiological resolution or improvement occurred in 94%. This discrepancy may be due to permanent neuronal damage which may go undetected using current neuroimaging techniques.

CONCLUSION

Although the syndrome of acute extrapyramidal movement disorders in uremic patients with bilateral basal ganglia lesions is rare, it is important to recognise especially in Asian diabetic patients with renal failure, as most cases will recover with appropriate supportive measures which includes increased dialysis.

Conflict of interest
On behalf of all authors, the corresponding author states that there is no conflict of interest.

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