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CLINICAL ROUNDS IN CHILD AND ADOLESCENT MENTAL HEALTH

Psychotic Symptoms in a Child with Long Standing SLE Nephritis: Neuropsychiatric Manifestation or Sequelae to Lupus?

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Abstract

Systemic Lupus Erythematosus (SLE) is a prototypic autoimmune disease of unknown etiology, which affects multiple organ systems including the central nervous system (CNS). Though not common, childhood onset SLE is a known and established entity. Neuropsychiatric symptoms are common in childhood onset SLE. Of these, psychosis and behavioural symptoms are relatively rare, and there is no consensus on the proper treatment of such cases. We report a case of 13-year-old boy, diagnosed with lupus nephritis, and presented with psychosis and behavioural symptoms. The highlight of this case is that the psychiatric symptoms were present despite the primary illness being quiescent. Thus, the patient was treated with Olanzapine and lorazepam, while continuing immunosuppressive therapy as previously. Also, MRI brain revealed vasculitic changes in the right hemisphere, which might be one of the etiological factors playing role in the development of these neuropsychiatric symptoms.

Key words: *systemic lupus erythematosus, psychotic symptoms, treatment*

Résumé

Le lupus érythémateux systémique (LES) est une maladie auto-immune prototypique d'étiologie inconnue, qui affecte de multiples systèmes organiques, dont le système nerveux central (SNC). Bien qu'il ne soit pas commun, le LES qui apparaît dans l'enfance est une entité connue et établie. Les symptômes neuropsychiatriques sont communs dans le LES qui apparaît dans l'enfance. Parmi ces symptômes, la psychose et les symptômes comportementaux sont relativement rares, et il n'y a pas de consensus sur le traitement adéquat de ces cas. Nous rapportons le cas d'un garçon de 13 ans, ayant reçu un diagnostic de néphrite lupique, et présentant des symptômes de psychose et de comportement. Le fait saillant de ce cas est que les symptômes psychiatriques étaient présents malgré que la maladie primaire fût dormante. Donc, le patient a été traité par olanzapine et lorazépam, tout en poursuivant une thérapie immunosuppressive comme auparavant. En outre, une IRM du cerveau a révélé des changements vasculitiques dans l'hémisphère droit, ce qui pourrait être l'un des facteurs étiologiques impliqués dans le développement de ces symptômes neuropsychiatriques.

Mots clés: *lupus érythémateux systémique, symptômes psychotiques, traitement*

Introduction

Systemic lupus erythematosus is a chronic autoimmune disorder affecting multiple organ systems and presenting with diverse clinical manifestations. Neuropsychiatric manifestation of SLE (NPSLE) is one of the major and most disabling presentations, and comprises of a wide range of neurological as well as psychiatric syndromes. Psychiatric manifestations like psychosis, anxiety, or mood disorder may occur as part of the primary disease process, or secondary to central nervous system sequelae of SLE, e.g. seizures, infection or adverse effect of treatment with steroids, or immunosuppressant (Mak, Ho, & Lau, 2009). Approximately, 15% of patients with systemic lupus erythematosus (SLE) will have the onset of their disease in childhood or adolescence (Tucker, 2007). Children with SLE have been shown to have a higher frequency of SLE-related renal

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disease, neurological and haematological complications (Tucker et al., 2008; Hersh et al., 2009). Although neurocognitive dysfunction has been shown to occur in 30-60% of children with SLE (Mina & Brunner, 2010), psychosis and behavioural symptoms are relatively less common in this age group (Sibbitt et al., 2002).

Case

We present the case of a 13 year old boy, diagnosed with Grade III lupus nephritis with hypertension and thrombocytopenia at the age of nine years. At the onset of illness, family members gave history of behavioural symptoms of acute onset, characterized by unprovoked anger outbursts, physical aggression, and few occasions of running away from home. Patient at this point of time was admitted under pediatric nephrology, and a brief consultation regarding the behavioural symptoms was sought from Consultation-Liaison wing of department of psychiatry. However, no psychotropics were prescribed. These behavioural symptoms subsided over two to three weeks when patient was treated with corticosteroids (up to 40 mg/day) for his primary illness. MRI brain, at the age of nine years, revealed diffuse cerebral atrophy, with periventricular white matter changes and hyperintensities around corpus callosum, suggestive of vasculitic changes. Patient was under regular follow up in pediatric nephrology since then. Azathioprine (up to 50 mg/day) and Hydroxycholoroquine (up to 200mg) were added subsequently after six months of initial treatment with corticosteroids following an exacerbation of lupus nephritis. Tab. Enalapril 2.5 mg was added for hypertension during the same period, which has been continued thereafter. No aggravation of behavioural symptoms had been noticed during this period. Patient maintained well over the next two years, although his academic performance gradually declined. At the age of 11 years, patient began to have episodes of generalised tonic-clonic seizures, once in every 15-20 days. During this period, there was a re-emergence of the behavioural symptoms in the form of anger outbursts and physical aggression. Patient was treated with Valproic acid (up to 600 mg/day), following which there was a decrease in the frequency of seizure episodes in every three to four months and the behavioural symptoms subsided over next four to six months. The dose of Valproic acid was tapered after 1.5 years and at the time of admission patient was on 400 mg Valproic acid, which has been continued thereafter. There have been no seizure episodes for the last 1.5 years. Patient was not referred to psychiatry for his behavioural symptoms during this period.

At the age of 13 years, patient's family members noticed that he would appear fearful, and occasionally report seeing figures, although he would not elaborate further. He would have crying spells, and his interaction with them decreased significantly. He did not show interest in his personal grooming, and would often pass urine in his clothes. He predominantly, appeared apathetic and did not show any emotional reactivity to his surroundings. He sometimes disrobed himself in front of others, and on occasion was found rubbing his private parts. Gradually over the next three to four weeks, he was completely unable to feed or groom himself, and required assistance from family members. He was referred to psychiatry from pediatric nephrology department due to further worsening of these symptoms, and was subsequently admitted. According to history given by parents, he was born out of a full term, normal delivery with no developmental delay in milestones (birth records were not available). He was of easy going premorbid temperament. There was no family history of any psychiatric disorder, connective tissue or autoimmune disorder. General physical examination revealed bilateral posterior sub capsular cataract and grade I clubbing. His height was 145 cm and weight 32 kgs. His blood pressure was 108/70 mm of Hg. Systemic examination revealed no specific abnormality. No focal deficit on central nervous system examination was found. In general appearance and behavior, patient was of thin built, and unkempt. He was alert and fully conscious, but appeared apathetic and had frequent crying spells, without any provocation. Eye to eye contact was not made, or sustained and rapport could not be established. It was not possible to communicate with him. He made stereotypical gestures with hands, and showed disorganized behaviour in the form of putting things in mouth, lying on the floor etc. His affect was blunted. He kept repeating some phrases and words, but could not answer the interviewer's questions; further mental status examination could not be carried out. A formal cognitive assessment was attempted, but it could not be carried out, as the patient became uncooperative and refused to communicate.

In blood investigations, complete blood count, liver function tests and serum electrolytes were within normal parameters; serum urea/creatinine was 17/0.4. A 16 channel EEG record, with 10-20 system of electrode placement, showed the background rhythm as 8-9 Hz, 30-4040µV; symmetrical dominant alpha rhythm, responsive to eye opening (Table 1). No epileptiform discharges were seen. Activation procedure added no information. Alpha dropout, VST and k complexes were seen as sleep markers. A repeat MRI brain showed changes suggestive of vasculitis in the right cerebral hemisphere (in the region of bilateral centrum semi-ovale), and multiple T2/FLAIR hyper intensities in a focal area in left thalamus (Figure 1). A routine CSF examination was normal for sugar, protein and cells. Anti NMDA receptor antibodies, anti VGKC antibodies were negative. ANA titre was 1:40, and anti dsDNA was 30 IU/L, serum C3 levels were 134 mg/dl, aCLIgM-2.0, and aCLIgG-3.4, LAC, VDRL and ANCA-negative. Since immunological markers did not indicate a flare in SLE activity, he was maintained on prednisolone (10mg), immunosuppressants (azathioprine 50 mg and Hydroxycholoroquine 200mg), and antihypertensive (Enalapril 5mg) as previously. Tab. Olanzapine 5mg/day was added for the behavioural symptoms, and increased to

Table 1. Laboratory analysis	
Haemoglobin	13.3 mg/dl
Leucocyte count	11.9 x 103
Platelet	224 x 103
Serum urea/creatinine	17/0.4
ESR	7 mm/hr
ANA	1:80
C3	134 Range: 70-240 mg/dl
ANCA	- ve
aCL-IgG	3.4 Range: 0-12 GPL Units/ml
aCL-IgM	2.0 Range: 0-12 MPL Units/ml
Anti-ds DNA	30 Range: 0-50 IU/ml
LAC	- ve
VDRL	-ve
Anti NMDAR (serum, csf)	-ve
Anti VGKC (serum, csf)	-ve
-ve = negative	

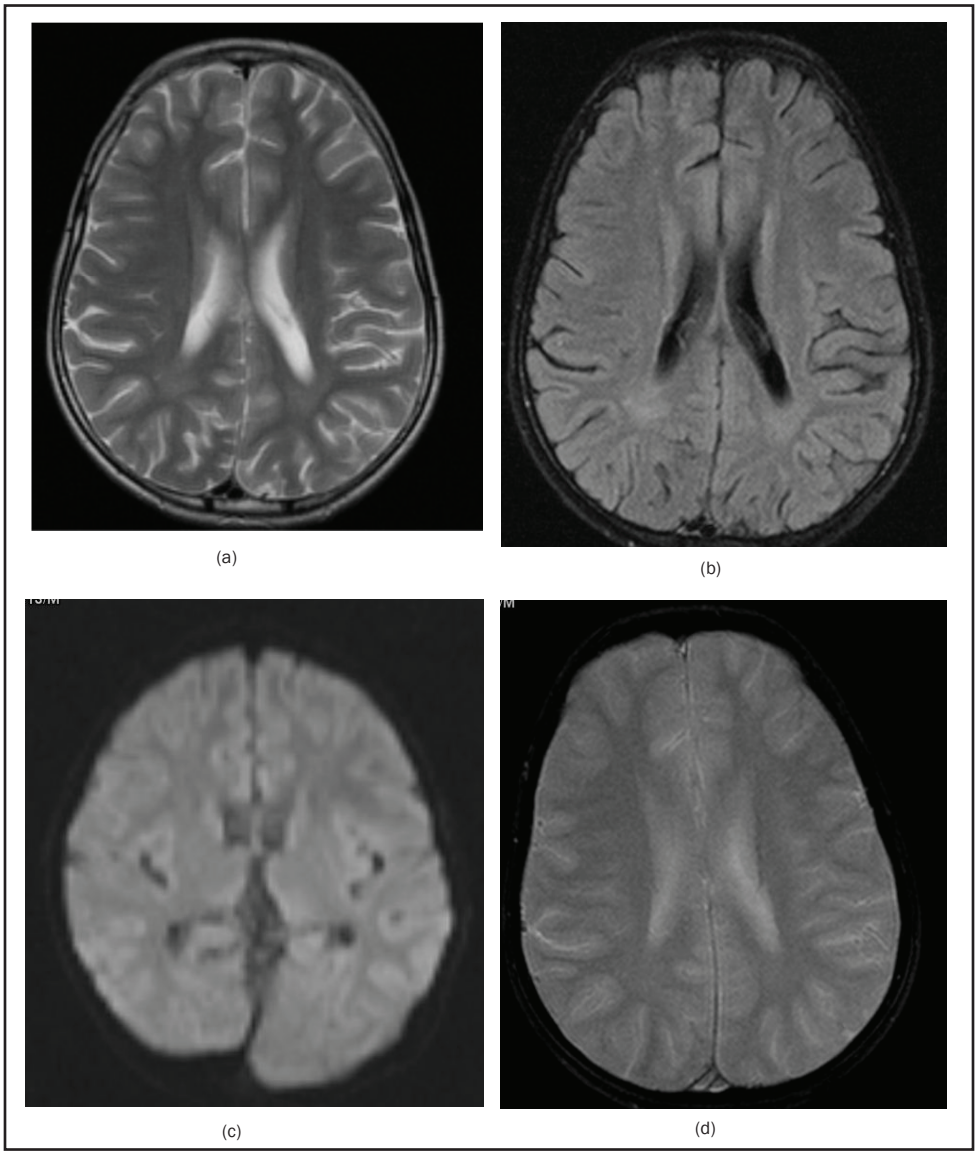
up to 20mg/day. Benzodiazepine (lorazepam 1.5mg/day), in divided dosage, was also added for the agitation. After instituting this pharmacological management, there was a significant improvement in patient's sleep and appetite over the next two months; he gradually started to feed himself, and self- care also improved. There was a decrease in the frequency of disorganized behavior, but intermittent crying spells, fearfulness, and anger outburst continued to persist. However, there was no improvement seen in affective blunting, and level of communication, even after six months of treatment.

As this patient hailed from a rural background of poor socio-economic status, assistance was taken from the Chief Medical Social Worker of the department to explore employment opportunities for the patient's father. Exemption of hospital charges were also made for the patient.

Discussion

The patient's symptoms can be explained from multiple perspectives. Presence of behavioural symptoms at the onset of illness, along with lupus nephritis points toward a neuropsychiatric manifestation of SLE. The fact that these symptoms improved once the treatment for SLE was instituted further lends support to it. The presence of findings suggestive of vasculitis on neuroimaging, points towards an etiological role of CNS vasculitis in the occurrence of neuropsychiatric symptoms. Cerebral vasculitis in SLE is rare phenomenon, and its incidence in post-mortem studies is less than 10% (Koerner, Sommer, Knauth, Breitbart, & Wildemann, 2000). Although cerebral vasculitis has been reported in lupus psychosis (Rowshani, Remans, Rozemuller, & Tak, 2005), its etiological significance is yet to be delineated There was worsening of the behavioural symptoms during onset of seizure episodes, which could have been a cluster of neuropsychiatric symptoms manifesting concurrently, or as a sequelae of the seizure episodes. Childhood onset SLE is a rare disease with an incidence of 0.3 – 0.9 per 100,000 children-years, and a prevalence of 3.3 – 8.8 per 100,000 children (Kamphuis & Silverman, 2010). A case series of ten paediatric SLE patients, with psychiatric symptoms and behavioural changes, showed that majority presented with withdrawal, confusion, bizarre and disorganized behaviour and abnormal sleep (Turkel, Miller, & Reiff, 2001). Another study found that up to 65% of childhood SLE patients develop NPSLE at any time during the disease course, and the most common neuropsychiatric symptoms were headache, mood disorder and cognitive dysfunction (Sibbitt et al., 2002) The prevalence of psychosis in childhood SLE has been found to be around 10%, and it is frequently concomitant with cognitive dysfunction, and acute confusional state (Benseler & Silverman, 2007). At the time of admission, our patient presented chiefly with apathy, disorganised behaviour, disinhibited behaviour and impaired self-care. However, patient's recent symptoms were not accompanied by an exacerbation of his SLE (as ascertained by immunological parameters being within normal limit), or an increase in doses of medication (steroids or immunosuppressant). Although many auto-antibodies have been found in SLE patients, none have been a good diagnostic marker, nor do they correlate well with disease activity. Anti-ds DNA antibody and antinuclear antibody (ANA) are the most frequently used markers at present (Wu et al., 2006). Neuropsychiatric symptoms have been known to manifest, even when SLE has been shown to be quiescent in other organ systems (Hanly et al., 2009). In a longitudinal study of patients with SLE conducted for nine years, primary

Figure 1. MRI



MRI brain axial T2W (a), FLAIR (b), DWI (c) and T2W GRE image (d) reveal small T2W/ FLAIR hyperintense foci in the right centrum semiovale, without any restriction of diffusion or any evidence of hemorrhage. They may represent vasculitic changes in the white matter

psychotic disorder was diagnosed in 17% of the cohort. Of the patients presenting with primary psychotic disorder, 66% of cases were related to NPSLE, 31% were associated with corticosteroids and 3% were related to neither NPSLE nor medication (Appenzeller, Cendes, & Costallat, 2008). No such data is available for paediatric population.

There are no controlled trials assessing any treatment strategy in the management of lupus psychosis. Several small studies have reported the benefit of the use of corticosteroids and different immunosuppressive strategies, especially cyclophosphamide in patients with NP lupus (Ramos, Mendez, Ames, Khamashta, & Hughes, 1995). Another study in seven paediatric SLE patients reported favourable outcome with aggressive treatment with combined intravenous methylprednisolone and cyclophosphamide, followed by monthly intravenous for severe NPSLE (Baca et al., 1999) .However, in the index case, since his neuropsychiatric manifestations were not accompanied with a flare in his immunological parameters or his primary illness (lupus nephritis), we decided to manage him symptomatically with antipsychotics and benzodiazepines.

Although a formal cognitive assessment could not be carried out, the patient's gradually declining academic performance could be indicative of progressive cognitive dysfunction, which is a common manifestation of neuropsychiatric SLE in children. Deteriorating cognitive function could also be hypothesised to be the cause for behavioural symptoms. Finally, structural imaging of the brain showed diffuse cerebral atrophy, and progressive vasculitic changes, which could be implicated for the enduring nature of the symptoms, despite giving adequate doses of antipsychotic medication. There is a lack of adequate literature on the outcome of psychosis due to lupus, more so in childhood SLE. A retrospective cohort study of adult patients with SLE, found that one year after the diagnosis and treatment, 60 and 40% of the patients with lupus psychosis showed complete resolution of their psychiatric symptoms or chronic psychotic activity, respectively (Pego-Reigosa & Isenberg, 2008). Prospective studies are required to delineate the predictors of long term outcome and optimize treatment.

Conclusion

Behavioural and psychotic symptoms, as a neuropsychiatric manifestation of SLE in children, are not well understood. Interplay of various mechanisms might have a role in emergence of these symptoms in paediatric SLE. Lupus-induced inflammation, ischemia, and direct autoantibody effects on gray and white matter structures may contribute to cognitive deficits observed in children and adults with SLE. Their role in pathophysiology of psychotic symptoms needs to be further elucidated.

Acknowledgements/Conflict of Interest

The authors have no financial relationships to disclose.

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