Case Report

Leukodystrophy Presenting as Hyperactivity and Bipolarity with Uncommon Adverse Drug Reaction

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ABSTRACT

Leukodystrophy is a group of demyelinating neurodegenerative diseases of brain with varied presentation and multiple etiologies. Prognosis is predominantly dismal. Misdiagnosis and wrong treatment are common in this group of rare neurological disorders, especially when it presents with psychiatric symptoms. In this case, importance of neurological and radiological evaluation and need for high diagnostic suspicion in treatment-resistant psychiatric disorders is highlighted.

Key words: *Adverse drug reaction, bipolar disorder, hyperactivity, leukodystrophy, lithium-induced neuroleptic malignant syndrome*

INTRODUCTION

Leukodystrophy is a group of disorders characterized by loss of normal myelin in white matter predominantly of genetic etiology.[1,2] These disorders vary in presentation, etiology, pathology, and prognosis. Some of the leukodystrophies can present with psychiatric symptoms. Due to rarity of such presentation, diagnosis is missed frequently leading to suffering of patients.

Relevant biomarker assay and genetic analysis are necessary for complete diagnosis and prognostication of leukodystrophies. With magnetic resonance imaging (MRI) assessment and clinical profile, a provisional diagnosis with reasonable accuracy can be made in most situations but not all.[3,4] Above all, clinical suspicion and awareness of possibility of such presentation are necessary.

We are reporting a case of treatment-resistant hyperactivity and bipolarity that presented with significant treatment-emergent adverse effects. It was diagnosed as a leukodystrophy with strong radiological suggestion of adrenoleukodystrophy.

CASE REPORT

A 13-year-old male child RB, born of nonconsanguineous parentage with no family history of psychiatric, neurological disorders, presented to child and adolescent

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psychiatry outpatient department (OPD) at our institute with generalized tremors of body, cogwheel rigidity, and restlessness since 1 month. History revealed new onset hyperactivity with declining school grades and decreased interest in going to school for 2 years. The child was treated with methylphenidate 10 mg/day and atomoxetine 18 mg/day for 6 months without any benefit in hyperactivity symptoms. Three months before presentation in our OPD, the child had a manic episode with over-familiarity, over-talkativeness, and increased psychomotor activity while on above-mentioned treatment regimen. The ongoing medications were stopped, and the child was treated with olanzapine (15 mg/day) and valproate (800 mg/day) for this episode. Child developed impaired mobility, drooling, and rigidity on antipsychotic medications and family had to stop all the medications for 5 days before visiting to our OPD. He was admitted for further management.

During admission, the child was started on trihexyphenidyl 6 mg/day, and lithium was introduced for mood symptoms. For next 3 days, tremors and subjective restlessness were not controlled but biological functions improved along with a reduction in mood symptoms. Intramuscular injection phenergan 50 mg was started as a treatment of refractory extrapyramidal syndrome. Meanwhile, on day 6 of inpatient (IP) care, creatine phosphokinase (CPK) levels were found to be high up to 1242 U/L, also child had pyrexia of 100°F. Blood pressure fluctuation and tachycardia (100 beats/min) were also noticed. Neuroleptic malignant syndrome (NMS) was a possible cause. Injection phenergan was stopped, and diazepam was started with adequate hydration and other symptomatic treatment. Considering differential diagnosis of anticholinergic-induced toxicity, anticholinergic medications were also stopped. On the next day, CPK levels increased to 1827 U/L. Lithium was stopped immediately (serum lithium 0.51 mEq/L) as lithium-induced NMS has been reported.[5] Child's alertness and mobility improved but behavioral symptoms such as crying spells, stubbornness, clinginess, and restlessness worsened after stopping lithium. Cerebrospinal fluid study result was not significant. Other metabolic parameters/investigations such as ammonia, lactate, tandem mass spectrometry, urine for abnormal metabolite, copper, and ceruloplasmin were within normal range. However, his MRI revealed T2-hyperintensities in the occipitoparietal region, internal capsule with involvement of optic fibers, T1 with contrast shown hypointense lesion with peripheral advancing edge enhancement, which was strongly suggestive of adrenoleukodystrophy [Figure 1] based on location and enhancement.[2,6] Endocrinology evaluation including early morning cortisol and adrenocorticotropic hormone level were within normal limits. Patient's family could not afford the cost of very long chain fatty acids and ABCD1 gene mutation testing.

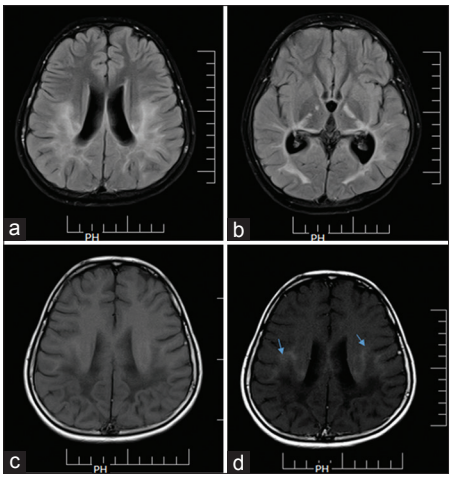

Figure 1: Magnetic resonance imaging images in axial section shows symmetric T2-hyperintense signal changes involving bilateral lobar and periventricular white matter extending to posterior limb of the internal capsule and optic radiation (a and b). The hypointense core of the lesion in T1 (c). The characteristic advancing margin enhancement on postcontrast T1-images (d) is a diagnostic feature of adrenoleukodystrophy

On day 14 of IP care, CPK level was normal (112 U/L), and the child was rechallenged with lithium for uncontrolled mood symptoms. On subsequent mental status examinations, the child improved in terms of mood symptoms such as unprovoked crying spells and agitation.

On day 18, CPK level found to be raised to 880 U/L while being only on lithium, hence lithium was stopped. Child was started on clonidine 100 μg/day gradually in 3 days.

His symptoms reduced within few days. He was discharged on this medication.

DISCUSSION

While reviewing the case, we noted that if the disease could be diagnosed early, then treatment options and prognosis would be different, and patient's suffering might be less. Alertness to clinical features leads to proper diagnosis earlier, if treating doctors are sufficiently primed about such possibility.

First of all, cognitive decline as tested by deficit in attention, memory, along with irritability, with new onset hyperactivity, and abnormal psychotic behavior could be a pointer toward possible organic pathology.[7-9] Absence of family history of mood

disorder, no identifiable precipitating factor also strengthened this possibility.

Among children with attention deficit and hyperactivity disorder, 90% respond to one class of medication or the other.[8] Hence, in case of nonresponse, other possibilities should be explored.

Resistant extrapyramidal side effect can be an indicator of identifiable organic pathology of brain as in this case. These side effects could be a result of disease progression hastened by antipsychotic medications. Unexplained progressive motor or mental symptoms in a young person may direct suspicion toward a leukodystrophy.[10] Likewise, mood symptoms can also be secondary to organic pathology such as adrenoleukodystrophy.

We cannot formally confirm the diagnosis as patient's family could not afford the biomarker and genetic analysis. However, the clinical picture and classical MRI findings strongly suggest a provisional working diagnosis.

It was an atypical presentation of parieto-occipital disease with optic radiation involvement presenting with cognitive and mood symptoms and without visual symptoms of blindness. It indicates that central nervous system pathology may not be strictly region specific; rather these symptoms depend on the association between different areas of the brain.

Lithium when used in conjunction with antipsychotics, arguably increases the chance of NMS,[11] but not in child and adolescent population.[12] Lithium alone can cause NMS in toxic concentration,[13] but only one case report of NMS caused only by lithium in normal blood levels could be found.[5] Patient in that report was an aged patient with multiple comorbidities and while on multiple medications. There it was thought that aged degenerating brain may be predisposed to more neurotoxicity to lithium. In this case, mild NMS that was precipitated by lithium fulfilled the challenge–dechallenge–rechallenge protocol[14] for adverse side effect determination. Such solely lithium-induced NMS is not reported before in this age group, and may be secondary to diseased brain that predisposed this child to neurotoxic effects of lithium. As there is no report of adrenoleukodystrophy presenting with bipolarity and treated with lithium in this age group, it is difficult to conclude if this disease can predispose the patient to side effects.

CONCLUSION

The awareness of the possibility of neurological diseases, in atypical presentations and treatment unresponsive pediatric patients with psychiatric symptoms, is very important for medical fraternity. We need to be extra cautious regarding possibilities of adverse drug reaction and neurotoxicity in such patients with neuropsychiatric disorders.

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Conflicts of interest
There are no conflicts of interest.

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