ADRENOLEUKODYSTROPHY: AN X-LINKED LEUKODYSTROPHY WITH PREDOMINENT NEUROLOGICAL MANIFESTATION : A CASE REPORT

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Summary

Leukodystrophy cases are not common in routine clinical practice. Among leuko-dystrophies adrenoleukodystrophy (ALD) cases are more common. It presents with neurologic and endocrine features with characteristic Megnetic Resonance Image (MRI) findings and biochemical changes. Early recognition of index case is important because dietary modification & supplementation with Lorenzo's oil can slow progression of the disease course and can be life saving. Bone Marrow Transplantation (BMT) if performed in earlier stage of disease can be very rewarding to show stabilization and in some instances improvement of patient's condition. More over prenatal diagnosis of affected boys can be performed by analyzing pedigree chart of an affected family members of this X-linked chromosomal disease.

Key words

Adrenoleukodystrophy; Cortical blindness; Bone marrow transplantation.

Introduction

Adrenoleukodystrophy (ALD) is a genetically determined X-linked recessive disorder characterized by progressive dysfunction of adrenal cortex and white matter of central and peripheral nervous system. Here key biochemical abnormality is the tissue accumulation of unbranched saturated Very Low Chain Fatty Acid (VLCFA) and excess hexacosanoic acid (C26:0) is the most striking and characteristic feature [1]. The adrenal dysfunction is probably a direct consequence of accumulation of VLCFA. The minimum incidence of X-ALD in male is 1/21,000 and combined incidence of X-ALD male and heterozygous female in general population is estimated to be 1/17,000 [1]. Moser and colleagues (1980), using clinical and biochemical criteria have identified the following subtypes of ALD [2]:

i) A progressive degeneration of cerebral white matter in young males, often with cortical blindness- the classic type accounting for half of all cases
ii) An intermediate form in juvenile or young adult males with cerebral and spinal involvement (5%)
iii) A progressive spinal cord tract degeneration in adult males (25%)
iv) A chronic mild, nonprogressive spastic paraparesis in heterozygous female carriers (10%)
v) Familial instances of Addison disease without neurologic involvement in males (10%)
vi) Possibly, in male infants a form originating at birth (eg. Zellweger disease)

Neurologic manifestations may develop in up to 50% of female carrier. The onset of spastic paraparesis tends to occur later in life usually in the third or fourth decade and progression tends to be slow [2].

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Case Report

Master X, 08 Years boy, second issue of a nonconsanguinous parents, with uneventful birth history admitted into neurology ward Chittagong Medical College Hospital (CMCH) with the complaints of gradual loss of vision & hearing for last 4 months. From his parents we came to know that with normal milestone of development and average school performance he was relatively well. Incidentally his parents noticed that he gradually became irritable, restless, hyperactive with reduced sleep at night and couldn't properly

copy blackboard writings in his school and couldn't here unless it was told very loudly associated with decline of his academic performance. These symptoms progressed day by day and when he was unable to see anything properly and didn't follow command due to high level of hearing defect his parents decided to admit him into hospital. After hospitalization he had several episodes of seizure. Throughout the course of illness there was no history of low grade fever, weight loss, cough, breathlessness, vomiting, skin pigmentation, painful eye events, head injury, limb weakness, bladder bowel involvement. None of his family members are affected with these sorts of symptoms. He was fully vaccinated under EPI schedule.

On examination he was restless, non cooperative. His pulse was 80 bpm, Blood pressure 110/70 mmHg without any postural hypotension or skin pigmentation. Except congenital clubbing all components of general examination were normal. On nervous system examination higher mental function couldn't be evaluated properly as he was quite restless, got gross hearing defect and unable to see properly with normal speech. Except bilateral cortical blindness (Absent PL/PR with normally reacting pupils and normal fundi) and bilateral sensorineural hearing loss all other cranial nerves were intact. Positive findings in motor system examination were reduced deep tendon reflexes and bilateral extensor plantar response. No abnormality detected in his sensory and cerebeller examination.

Regarding investigations all of his routine tests including CXR P/A view, ECG, Echocardiography were normal. Serum electrolytes, cortisol and Adrenocorticotrophic Hormone (ACTH) level were normal during first assessment in neurology ward after 4 months of his symptom onset. Pure tone audiogram revealed bilateral total deafness. MRI of brain showed abnormal posterior periventricular hyperintensity (In T2 & FLAIR image) extending across the splenium of corpus callosum suggestive of leukodystrophy probably adrenoleukodystrophy.

The patients has got definite and undoubted history and clinical evidence of doctor witnessed true Generalized Tonic Clonic Seizure (GTCS) and reduced deep tendon reflexes as the manifestation of Peripheral Neuropathy (PN).

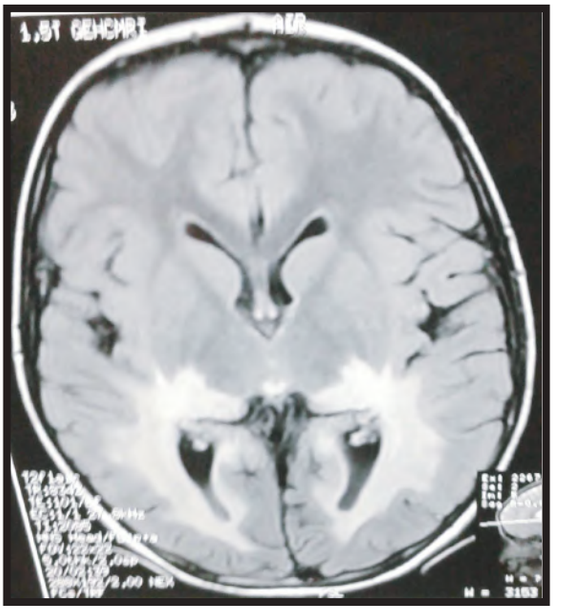

Fig 1 : FLAIR image of brain MRI showing hyper intensity involving posterior periventricular white matter

Moreover his parents were poor to afford other costly investigation. So Electroencephalogram (EEG), Nerve Conduction Study (NCS) were not requested to establish presence of seizure and PN. The specific laboratory marker of the disease is an excess of Very Long Change Fatty Acid (VLCFA) in particular absolute level of hexacosanoic acid (C26) & the ratio of C26 to C22 (Docosahaxanoic acid, C26: C22) and of C24 (Tetracosanoic acid) to docosahaxanoic acid (C24: C22) in plasma erythrocytes or leukocytes or cultured fibroblasts. As this investigation is not available in our country so these parameters couldn't be assessed.

Discussion

Among the varied X-ALD childhood cerebral form is most common. Symptom onset usually in between the ages of 4-8 years [3]. The most common initial manifestation is hyperactivity which is often misdiagnosed as Attention Deficit Hyperactivity Disorder (ADHD) and worsening of previous good academic school performance. Auditory discrimination is often impaired [4]. Other initial symptoms are disturbance of vision, seizure, poor handwriting. Visual disturbance are often due to involvement of cerebral cortex, which leads to variable and seemingly inconsistent visual capacity. In most patients adrenal dysfunction is recognized only after the condition is diagnosed

because of cerebral symptoms. Cerebral childhood ALD tends to progress rapidly with paralysis, visual and hearing loss associated with loss of ability to speak and swallow. In all phenotypes development is usually normal in the 1st 3-4 yr of life. There is evidence that variations in methionine metabolism may contribute to the phenotypic variability in adrenoleukodystrophy/ adrenomyeloneuropathy (ALD/AMN) complex [5,6,7]. ALD is characterized by inflammatory demyelination resulting in confluent bilaterally symmetrical loss of myelin in cerebral & cerebeller white matter. The parieto-occipital region is usually affected first [8,9].

The reported case was a boy of 8 years with good school performance, normal milestone of development admitted in hospital with neurological symptoms of hyperactivity, restlessness, progressive visual and hearing loss with decremental school performance. After clinical evaluation and investigational support we got positive clinical clues of recent onset but rapidly progressive neurological manifestations, features of ADHD for which he was very restless, noncooperative during examination, bilateral cortical blindness, bilateral sensorineural deafness and seizure without any significant clinical and biochemical aberration of adrenal dysfunction. Clinically neurological and endocrine system examination of his mother and sister reveled no abnormality.

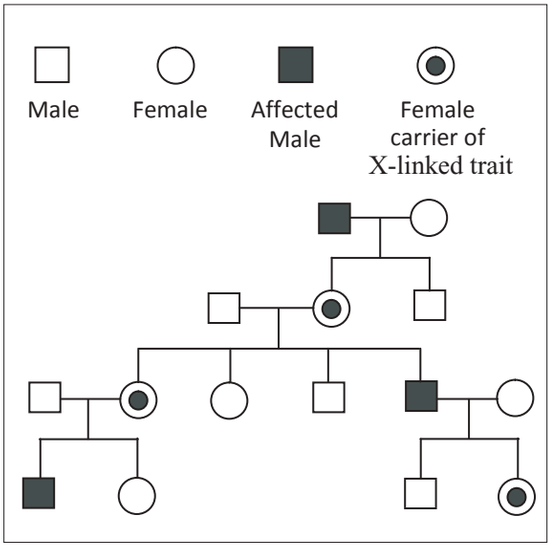

Fig 2 : Pedigree Chart, X-linked inheritance

Regarding investigational clues in MRI brain there was features of leukodystrophy almost symmetrically involving white matter in posterior periventricular region without any evidence of poliodystrophy. Pure tone audiogram revealed bilateral total deafness. Another leukodystrophy named metachromatic leukodystrophy which is an autosomal recessive white matter disease caused by Arylsulfatase A (ASA) deficiency could be a possibility in this case. But the juvenile form of metachromatic leukodystrophy presents with gait disturbance, mental deterioration, urinary incontinence, emotional difficulties and got a more indolent course. Features of uncommon leukodystrophy called orthochromatic leukodystrophy are cerebellar ataxia, frontal lobe type of dementia and epilepsy. So after total evaluation of onset, characteristic clinical features, tempo of disease progression investigational findings X-linked childhood cerebral form of adrenoleukodystrophy is likely diagnosis.

There is no correlation between the neurologic phenotype and the nature of the mutation on the severity of the biochemical defect as assessed by plasma level of VLCFA or between the degree of adrenal involvement and nervous system involvement [1]. The severity of the illness and rate of progression correlate with the intensity of inflammatory response. Approximately half of the patients do not experience the inflammatory response. A modifier gene that sets the “thermostat” for the inflammatory response is postulated.

Confirmatory laboratory investigation is excess of VLCFA in plasma, erythrocytes or leukocytes or cultured fibroblast [10].

This investigation could have added point to our diagnosis but unfortunately this investigation is not available in our country. As we reported his features only after 4 months of symptom onset clinical features and /or biochemical changes of adrenal insufficiency would be evident later on which is not uncommon in childhood cerebral form of ALD as mentioned earlier.

Different components of management include corticosteroid replacement for adrenal insufficiency or adrenocortical hypofunction which may be life saving and increase general strength and well being but doesn’t alter the course of neurologic disability, BMT which has

been shown to stabilize the disease and reverse some of the MRI charges if done in earlier stage of ALD, Lorenzo's oil (4:1 mixture of glyceryl trioleate and glyceryl trierucate) combined with a dietary regimen enriched with monounsaturated Fatty Acids (FA) and devoid of long chain FA is recommended for neurologically asymptomatic boys who have a normal brain MRI and are younger then 8 years old [1]. Lorenzo's oil has not been shown to alter disease progression in already cerebral involved cases.

Prenatal diagnosis of affected male fetus can be achieved by measurement of VLCFA levels in cultured amniocytes or chorionic villus cells and by mutation analysis.

Conclusion

It is to be said that X-ALD should be considered in differential diagnosis of childhood onset progressive visual, auditory and cognitive impairment with or without overt manifestation of adrenal dysfunction.

Disclosure

All the authors declared no competing interest.

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