Unusually prominent horizontal gaze palsy in a case of Niemann-Pick type C disease

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Abstract

Niemann-Pick Type C disease (NPC) is a rare inherited metabolic disorder characterized by lipid accumulation and systemic manifestations due to multiple organ involvement. Only a few cases of NPC have been reported so far from India. Varying presentations and often lack of access to complex diagnostic tests have leaded to initial misdiagnosis on few occasions. We here report a provisionally diagnosed case of NPC with prominent horizontal gaze palsy along with characteristic vertical gaze palsy and normal findings on microscopic examination of skin biopsy specimen.

Key Words

Niemann-Pick Type C disease, gaze palsy, sea blue histiocyte

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Introduction

Niemann-Pick Type C disease (NPC) is a lysosomal storage disorder due to defect in intracellular cholesterol trafficking and consequent accumulation and sequestration resulting in neuro-visceral complications. The wide spectrum of manifestations along with difficult diagnostic protocol warrants need for increased awareness about this rare condition. We here report a case of juvenile onset neuropsychiatric symptoms with bone marrow findings of sea blue histiocytosis suggestive of the diagnosis of NPC.

Case Report

A 27-year-old lady, product of non-consanguineous marriage with uncomplicated birth history was apparently normal until 11 years of age. Symptoms started with worsening of school performance. The parents observed abnormal behavior in the form of restlessness, hallucinations, unprovoked episodes of screaming and crying, and decreased social interaction. Simultaneously, there was gradual onset of neurological symptoms accompanied by cognitive decline. The patient developed involuntary movements and abnormal posturing of limbs. Gradually progressive dysarthria and difficulty in walking due to clumsiness and impaired coordination interfered with patient's ability to lead an independent life.

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Family history records death of elder sibling of the patient at age of 28 years due to chronic disease. He had symptoms of progressive motor and cognitive decline and was diagnosed to have storage disorder following bone marrow examination. Unfortunately, clinical data in details was not available.

On examination, patient was conscious and oriented and the vitals were stable and initial survey revealed presence of generalized choreiform movements. Eye movement abnormality included both horizontal and down-gaze palsy [Video 1]. Other findings included generalized dystonia with prominent tongue and limb dystonia [Video 2]. Gait was characterized by short steppage, wide based with variable stride length [Video 3]. Deep tendon reflexes were brisk in all four limbs.

Routine investigations were unremarkable. Complete blood counts including platelet count were normal and there was no evidence of organomegaly on ultrasound imaging. Magnetic resonance imaging of brain showed cortical atrophy, ex-vacuo dilatation of ventricles and prominence of sulci and gyri [Figure 1]. The infra-tentorial structures were relatively spared except for mild cerebellar atrophy. Bone marrow

aspiration cytology demonstrated sea blue histiocytes implying lysosomal storage disorder [Figures 2,3]. No abnormality was seen on microscopic examination of skin biopsy specimen. Considering progressive neurodegenerative features along with characteristic bone marrow findings a provisional diagnosis of juvenile onset NPC was considered.

Discussion

NPC observes marked clinical heterogeneity varying from neonatal fatality and isolated hepatosplenomegaly in juvenile forms, to adult onset chronic neurodegenerative features. However, no evidence of organomegaly was noted in our case. Similar finding of absent visceromegaly have been documented in adult onset NPC.[1] While organomegaly due to lipid storage may be absent in up to 15% of all patients,[2] possible regression of systemic signs with age[2] could also explain our findings in juvenile onset type.

Neuropsychiatric involvement is a hallmark of this metabolic disorder. Psychosis followed by neurological manifestations as in our case has been concordant with the clinical profile of NPC patients.[3,4] We considered motor signs like dysarthria, supranuclear gaze palsy and severe dystonia in favor of our diagnosis.

Vertical supranuclear gaze palsy (VSGP) has been described as the characteristic eye movement disorder in NPC. In our patient, in addition to down-gaze palsy, there was also absence of horizontal saccades. Increased susceptibility of neuronal cells in the rostral interstitial nuclei of the medial longitudinal fasciculus has been suggested in pathogenesis[5] of VSGP in NPC. Horizontal gaze palsy has been rarely documented for cases with NPC. Abel *et al*. reported a range of horizontal saccade deficits in three patients with NPC and suggested that ocular motor measures can be index of disease severity.[6] Their study observed involvement at brainstem and prefrontal levels of control of horizontal saccades. Prominent horizontal gaze palsy in the present case may be because of involvement of frontal lobe. The imaging has revealed cortical atrophy including, frontal lobe degeneration with relative sparing of infratentorial structures.

Histopathology plays a key role in diagnosis of NPC. Bone marrow aspiration cytology for our case revealed sea blue histiocytosis suggestive of lipid metabolic disorder.[7] However, histological examination from skin biopsy specimens showed no abnormality. Mere electron microscopy has been proved to be of limited significance for diagnosis of NPC.[8] The recent guidelines suggest the integrated results from filipin staining of cultured skin fibroblasts in cholesterol rich medium along with genetic mutation studies as the gold standard diagnostic tests.[9] Unfortunately, we were not able to do these tests and even so, presence of clinical scenario comparable with other diagnosed cases that have been reported, and characteristic bone marrow findings[10] leave little room for alternative diagnosis. We may explain negative skin biopsy in our case as a 'variant biochemical phenotype' that may not show typical storage pattern in fibroblasts.[2]

At present, no standard blood tests or other simple procedures are available to diagnose NPC. Varying and

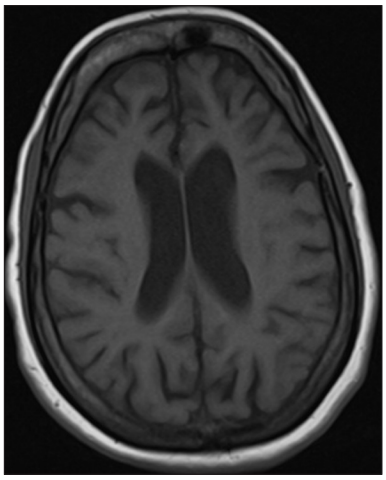

Figure 1: T1-weighted axial MRI-scan of the brain showing cortical atrophy and ex-vacuo dilatation of lateral ventricles

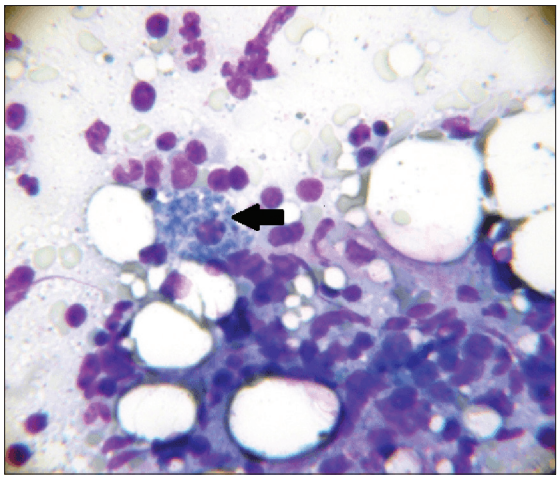

Figure 2: High power view of bone marrow aspirate smear, showing normal cellularity with normoblastic maturation and presence of sea blue histiocyte (marked with arrow) which is characteristic of Niemann-Pick disease

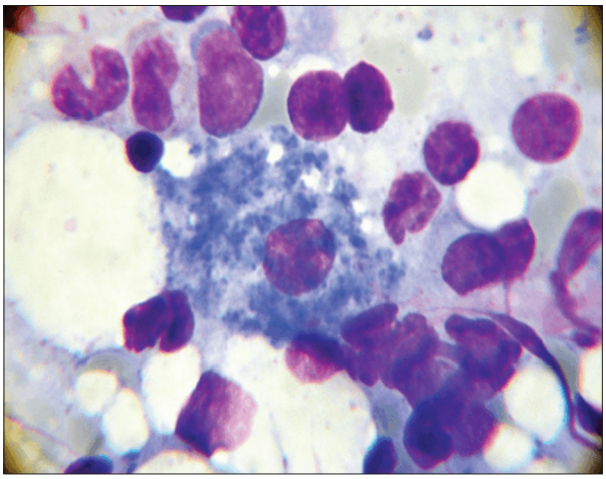

Figure 3: Higher magnification photomicrograph of sea blue histiocyte: The cell is around 25-30 microns in size with a relatively small nucleus and vacuolated blue colour cytoplasm

often delayed presentation has lead to initial misdiagnosis on few occasions.[4,11] The sophisticated diagnostic techniques and recently approved treatment being unavailable in India, increased knowledge and better understanding of clinical profile might help in early diagnosis and secondary prevention of complications. Our case report is an attempt to document a case of NPC with unusual eye movement sign of horizontal gaze palsy in addition to the well-known vertical gaze palsy. NPC should be considered as a differential diagnosis for any young onset gradually progressive neuropsychiatric manifestations with motor and eye movement abnormalities.

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