Childhood Ataxia with Cerebral Hypomyelination (CACH) syndrome: A study of three siblings

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We report a family of three siblings with Childhood Ataxia with Cerebral Hypomyelination. All the siblings presented with early onset cerebellar ataxia beginning around five years of age with mild mental retardation. MRI showed diffuse white matter signal changes in all three patients with cerebellar atrophy while the spectroscopy was abnormal only in the eldest who was the most severely affected. The cases are reported for their rarity as well as for an opportunity of observing this uncommon disease in its stages of evolution in three siblings.

Key Words: Childhood ataxia, hypomyelination, MRI, spectroscopy

Introduction

The syndrome of Childhood Ataxia with Cerebral Hypomyelination (CACH) was first reported by Schiffman in 1992. Though the early cases described were female with early childhood onset, it soon became evident that both sexes were affected and onset of disease could occur during late childhood and adolescence. Diagnostic criteria consist of normal early motor and mental development with a chronic progressive or episodic course of neurological deterioration with cerebellar ataxia and spasticity as the major symptoms, and the MRI showing symmetric involvement of the cerebral white matter with varying degrees of cerebellar atrophy. CACH is associated with mutations at the 3q27 locus. The eukaryotic translation initiation factor 2B (eIF2B) is composed of 5 different subunits and mutations have been described in each of these 5 subunits.

MRI abnormalities may precede symptom onset. The abnormal cerebral hemispheric white matter signals are homogenously increased on heavily weighted T2, low signal intensity on T1, and partially high and partially low signals on proton density images. On proton density or FLAIR images, both, CSF intensity lesions as well as rarefaction of white matter are seen. A fine meshwork of strands with a characteristic radiating pattern on sagittal and coronal images is seen in areas of CSF-like white matter. There is mild atrophy of the cerebral hemispheres and the cerebellum, especially the vermis shows varying degrees of atrophy. Corpus callosum, internal capsule, thalami, basis pontis and pyramidal tracts are involved. The globus pallidus shows markedly low signal intensity on T2 weighted images. Sequential MRIs reveal increase in CSF-like white matter areas, signal abnormalities of the U fibers and some cortical atrophy. Van der Knapp has termed this as “The Disease of the Vanishing White Matter”. MR spectroscopy data shows reduced N-Acetyl Aspartate [NAA], choline and creatine peaks in advanced cases though variations exist.

Histopathology showed rarefaction of cerebral white matter with increasing involvement of the deeper layers, especially adjacent to the lateral ventricles. The axons as well as the myelin sheaths are affected. The radiations seen in the cystic CSF-like spaces represent dilated vessels with processes of reactive astrocytes. Abnormal foamy oligodendroglial cells are identified by light and electron microscopy and are unique to CACH.

In this paper, we report the clinical and investigative observations on three siblings having this rare disease.

Case Report

The proband was a 12-year-old male born to non-consanguinous parents with normal early motor and mental development. He developed progressive gait ataxia since age 5, followed by incoordination of the upper limbs and slurred speech. He did not have any paresthesiae, sensory loss, radicular pains or sensory ataxia. There was no history of sphincter or cranial nerve involvement. He had a poor scholastic record and his teachers remarked upon his hyperactive behavior and inability to sit still in the classroom. However, he...
interacted well with his peers during play and could carry out all activities of daily living independently. There was no history of seizure activity. He did not have any history of head trauma or episodic worsening after a febrile illness. He did not have any malabsorption, frequent sinopulmonary infections or any cardiac symptoms. An older sister was normal but his two younger siblings were similarly affected.

On examination, the patient was short-statured with a normal head circumference (51 cm). General examination did not reveal any telangiectasias, thickened nerves, skeletal deformity, subcutaneous nodules or organomegaly. Formal IQ using Kamat scale was 45 though social conduct was relatively well preserved. He was hyperactive with attention deficit disorder. Speech was slurred. Fundii did not show evidence of optic atrophy, retinitis pigmentosa or cherry red macula. External ocular movements were full with normal saccades and jerky pursuit with impersistence of gaze. There was no nystagmus. The rest of the cranial nerve examination was normal. There was no spasticity but incoordination was noted in both upper and lower limbs, the latter being more severely affected. Rhomberg’s sign was absent and the sensory system was completely normal. All deep tendon reflexes were absent and the plantar responses were flexor. Routine hematological and biochemical investigations were normal. Acanthocytes were not seen in the peripheral blood smear and the lipid profile was normal. Serum IgA, alphafetoprotein levels and vitamin E levels were normal. Lactate and pyruvate levels were not raised. Leukocyte Beta galactocidase levels by fluorometric estimation were normal and leukocyte arylsulfatase A levels by photometric estimation were marginally reduced. However, urinary examination did not reveal presence of metachromatic granules. CSF was normal. The ECG and Echo cardiogram was normal. Nerve conduction studies failed to reveal any abnormality.

MRI demonstrated diffuse frontoparietal hypointensities on T1 (Figure 1) and hyperintensities on T2 weighted sequences (Figure 2) with cerebellar and cerebral atrophy (Figure 3). The corpus callosum was thinned out and the posterior limb of the internal capsule and the external capsule showed signal abnormalities. The globus pallidus showed hypointense signals on T2 weighted images. MR spectroscopy showed reduced NAA peak with normal creatine and choline peaks in the white matter (Figure 4).

The two younger siblings, a sister of 9 years and a brother 7 years of age, showed similar clinical features with progressive cerebellar ataxia starting at age 5 with mild mental retardation, absence of

**Figure 1:** T1 weighted MRI showing signal change in the cerebral white matter. **Figure 2:** T2 weighted MRI showing signal change in the cerebral white matter. **Figure 3:** T2 weighted MRI showing cerebral and cerebellar atrophy

**Figure 4:** MR spectroscopy of white matter showing reduced NAA peak in the eldest sibling

**Figure 5:** MR spectroscopy of white matter showing normal spectra in the youngest sibling.
spasticity and loss of deep tendon reflexes. However, the ataxia was not as marked. The MRIs of the two siblings showed similar white matter change with cerebral and cerebellar atrophy. However, the MR spectroscopic findings were normal in the two younger siblings (Figure 5).

**Discussion**

In our case, three affected siblings with normal parents points to an autosomal recessive mode of inheritance. MRI findings of widespread cerebral white matter involvement with cerebellar atrophy, which is characteristic of the syndrome of Childhood Ataxia with Cerebral Hypomyelination, exclude other causes of early onset cerebellar ataxia. Spasticity has been considered as one of the major clinical signs in this syndrome. The lack of spasticity in our patients was intriguing. Electrodiagnostic studies excluded associated neuropathy.

The spectroscopy was abnormal only in the eldest sibling with reduced NAA peak suggestive of neuronal loss. The choline and creatine peaks were normal and a lactate peak was not seen. In the other two siblings, though the MRI showed signal changes in cerebral white matter with cerebellar atrophy, the MR spectroscopy was normal which indicated that the spectroscopic changes occur later in the disease course. Though initial data showed reduction in all metabolites on MR spectroscopy, Van der Knaap later described four patients who had reduced NAA to creatine ratio while choline to creatine ratio was normal in three and elevated in only one patient.

CACH is widely believed to be a white matter disease. However, MR spectroscopy of white matter in demyelinating disorders shows an increase in absolute choline and in Cho:Cr related to enhanced membrane turnover. Since Van der Knaap found low NAA and normal Cho:Cr ratios in her patients, she has postulated that a primary axonopathy underlies the vanishing of the white matter. Selective and symmetric involvement of the brainstem tracts such as the central tegmental tracts may be considered as additional evidence in favor of a primary axonopathy. We plan to follow up these patients clinically and with serial MRIs and MR spectroscopies to know more about this uncommon disease with the passage of time.

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**References**


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