# Treatable Ataxia: a comprehensive case series study

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**Abstract**

Autosomal recessive cerebellar ataxias are a group of heterogeneous early-onset progressive disorders that some of them are treatable. We performed 4-year-follow up for 25 patients that considered as treatable ataxia in the literature. According to our study, patients would benefit from early detection of treatable ataxia, close observation, and follow-up.

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**Keywords:** ataxia, treatable, children

**Introduction:**

Ataxia in children is a common clinical sign of various disorders consisting of discoordination of movement with an absence of muscle control during voluntary activity. Ataxia is generally caused by disorder in function of the complex circuitry connecting the basal ganglia, cerebellum, and cerebral cortex, and this is known as "cerebellar ataxia." A wide variety of disorders can lead to acquired and inherited ataxia. Prompt identification of etiologies in progressive ataxic disorders is important, because corrective treatments may halt the degenerative process and preserve cerebellar functioning. (1) Some causes of ataxia in children and adolescents which are treatable include coenzyme Q10 (CoQ10) deficiency, ataxia with vitamin E deficiency (AVED), Niemann-Pick Type C (NPC) disease, Friedrich's ataxia, and Cerebrotendinous xanthomatosis (CTX). (2)

Primary coenzyme Q10 (CoQ10) deficiency is a group of cerebellar ataxias with mitochondrial respiration disorders caused by autosomal recessive multi genetic mutations. The features of primary CoQ10 deficiency include early-onset exercise intolerance, progressive cerebellar ataxia, intellectual disability, seizure, stroke-like episodes, mitochondrial myopathy, hypogonadism, and steroid-resistant nephrotic syndrome, with the age at onset ranging from infancy to late adulthood. (3) CoQ10 measurement in skeletal muscle and replacement with CoQ10 30 mg /kg/day orally can be helpful. (2)

Ataxia with vitamin E deficiency (AVED) is a rare, autosomal recessive neurodegenerative disorder, with mutations in the gene encoding the a-tocopherol transfer protein (TTPA/aTTP) result in defective transportation out of the liver and systemic vitamin E deficiency. (4) Diagnostic test includes vitamin E levels and treatment is by vitamin E (800 mg/d) in divided doses. (2)

Niemann-Pick Type C (NPC) disease is a rare genetic neurodegenerative disease with clinical spectrum ranges from a prenatal disorder to an adult-onset. The scarcity of the disease and the lack of expertise may result in misdiagnosis, delayed diagnosis, and inadequate care. This causes more physical, psychological, and intellectual deficits, inappropriate treatment, and patient disempowerment. The diagnosis of NPC is accompanied by improved quality of life if a diagnosis is made promptly and appropriate comprehensive management is instituted. (5) Serum oxysterol and NPC gene testing are considered as diagnostic tests and treatment by Miglustat 600mg/day may be useful. (2)

Friedrich's ataxia is characterized typically by progressive gait and limb ataxia, loss of deep tendon reflexes, and dysarthria, hypertrophic cardiomyopathy, diabetes, scoliosis, distal wasting, optic atrophy, and sensorineural deafness. (6)

Cerebrotendinous xanthomatosis (CTX) is an autosomal recessively inherited lipid storage disorder due to mutations of the CYP27A1 gene result in defective enzyme activity of sterol 27-hydroxylase which catalyzes the first step in the process of cholesterol side-chain oxidation. It causes impaired primary bile acid synthesis, increased concentration of bile alcohols, and increased formation of plasma and tissue cholestanol. The symptoms of CTX are produced in part by the accumulation of cholestanol and cholesterol in almost every tissue of the body, particularly in the nervous system, atherosclerotic plaques, and tendon xanthomata. Characteristic features of CTX include intellectual disability, dementia, pyramidal and/or cerebellar signs, peripheral neuropathy, and psychiatric disturbances. Xanthomas often appear in the second or third decade. As the progressive neurological findings present in early adulthood, initial symptoms consist of prolonged neonatal jaundice, chronic infantile diarrhea, and juvenile cataract. Brain imaging of patients reveals both supra and infratentorial atrophy and parenchymal lesions in periventricular white matter, globus pallidus and internal capsule, dentate nuclei, and cerebellar white matter. (7)

Here, we provide the clinical presentation, genetic findings, treatment, and outcome of 25 patients with treatable ataxia during the last 4 years.

**Patients and Methods:**

During 4 years period of study 135 patients of early-onset ataxia were registered that 25 patients with treatable ataxia were evaluated during the last 2-4 years, from 2017 to 2021. After detailed clinical and laboratory evaluation and exclusion of acquired causes of ataxia, they were subjected to whole-exome sequencing (WES) followed by confirmation of sequence variants using Sanger sequencing. Then, patients who had treatable ataxia(2) with genetic confirmation entered our study. We administered the drug of choice depending on the type of ataxia and followed patients regularly. Then we recorded related data including age, sex, onset of ataxia, additional features, age of definite diagnosis, genetic testing results, type of treatment, and outcome.

**Results:**

During 4 years period of study 135 patients of early-onset ataxia were registered that 25 of them were treatable autosomal recessive cerebellar ataxia. We followed 6 cases of Friedrich's ataxia, 3 cases of AVED, 2 cases of Co Q10 deficiency, 6 of NPC, and 8 cases of CTX. Among FA patients, 3 were males and one of them had a sibling with similar symptoms.

All 3 girls with AVED, 2 were siblings and they had a steady situation with vitamin E supplement. We also, reported 2 girls with co Q10 deficiency, one of them had refractory epilepsy irresponsible to high doses of co Q10 and anticonvulsant and became ventilator dependent.

Of 6 NPC patients, 4 were girls and 2 of them were siblings. Half of them experiences deterioration and half had no change in their condition despite miglustat use. Of 8 patients with CTX, 5 were girls and 6 were

Siblings. Other major-related data are presented in table1. Figure 1 shows significant MRI findings of 2 patients with CTX and Co Q10 deficiency.

**Discussion:**

Some treatable ataxia, include coenzyme Q10 (CoQ10) deficiency, ataxia with vitamin E deficiency (AVED), Niemann-Pick Type C (NPC) disease, Friedrich's ataxia, and Cerebrotendinous xanthomatosis (CTX). In this study, we followed patients especially children with treatable ataxia for 2 to 4 years. (2)

In a study, a 35-year-old patient with early-onset exercise intolerance and progressive cerebellar ataxia, wide-based gait, and tremor at 13 years of age with symptoms of dysautonomia was reported. Compound heterozygous mutations in the COQ8A gene were confirmed by WES. After treatment with ubidecarenone for 2 years, the symptoms significantly improved. (3) In a 2-year-follow up, one of our patients improved with high doses of co Q10, however, another patient who was a 13-year-old girl, with ataxia from 2.5 years of age and co Q10 usage for 2 years experienced super refractory epilepsy and vegetative state with ventilator dependence.

In a randomized controlled study, the efficacy of miglustat in the treatment of NPC was evaluated in comparison with standard care. Patients received miglustat at a dose adjusted for body surface area. The primary endpoint was horizontal saccadic eye movement (HSEM) velocity, considering its correlation with disease progression. Findings At 12 months, HSEM velocity had improved in patients received miglustat versus those receiving standard care. Children showed an improvement in horizontal saccadic eye movement (HSEM) velocity of similar size at 12 months. Improvement in swallowing ability and a slower deterioration in the ambulatory index was also seen in treated patients older than 12 years. (9) All our 6 patients were treated with miglustat and after 2 years of treatment, 3 of the patients showed improvement in the ambulatory index and others experienced deterioration during the time.

In a review of 194 CTX cases (ages ranging from newborn to 67 years old), the most common neurological abnormalities were corticospinal tract abnormalities including weakness, hyperreflexia, spasticity, Babinski sign (59.8%), ataxia (58.8%), cognitive disorder (46.4%), and gait abnormality (38.1%); 68 (35.0%) had baseline cognitive problems. Of our 8 patients, 7 suffered from ataxia and the mean age of onset was 20.14(ranged from 9 to 41-year-old). Cataract as an early manifestation (mean age of onset: 7.71 years, ranged from 3 to 13-year-old) and learning disorder were seen in 7 patients (one of them had baseline psychomotor retardation), and the other patient who was diagnosed in 42-year-old, had memory problems. One patient had a severe obsession and one suffered from depression. Hyperreflexia, spasticity, and Babinski sign were detected in 6 patients. Unfortunately, one patient who was diagnosed at 19-year-old, died 2 years after stem cell transplantation with a clinical picture of aspiration pneumonia. (10)

**Conclusions:**

According to our study, patients would benefit from early detection of treatable ataxia, therefore, the diagnostic approach should be more focused on these types of ataxia to achieve better treatment outcomes and decrease the burden of these diseases. Besides, like any chronic disease, close observation, and follow-up is important for this goal.

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