Ataxia telangiectasia

Ataxia telangiectasia (AT or A-T), also referred to as ataxia telangiectasia syndrome or Louis–Bar syndrome, is a rare, neurodegenerative, autosomal recessive disease causing severe disability. Ataxia refers to poor coordination and telangiectasia to small dilated blood vessels, both of which are hallmarks of the disease.

see Ataxia telangiectasia mutated.

A-T affects many parts of the body:

It impairs certain areas of the brain including the cerebellum, causing difficulty with movement and coordination.

It weakens the immune system, causing a predisposition to infection.

It prevents repair of broken DNA, increasing the risk of cancer.

Symptoms most often first appear in early childhood (the toddler stage) when children begin to sit or walk. Though they usually start walking at a normal age, they wobble or sway when walking, standing still or sitting. In late pre-school and early school age, they develop difficulty moving their eyes in a natural manner from one place to the next (oculomotor apraxia). They develop slurred or distorted speech, and swallowing problems. Some have an increased number of respiratory tract infections (ear infections, sinusitis, bronchitis, and pneumonia). Because not all children develop in the same manner or at the same rate, it may be some years before A-T is properly diagnosed. Most children with A-T have stable neurologic symptoms for the first 4–5 years of life, but begin to show increasing problems in early school years.

Patients with identified genetic diseases (ataxia-telangiectasia, chorea-achantocytosis, dopa-responsive dystonia, congenital nemaline myopathy, methylmalonic aciduria, neuronal ceroid lipofuscinosis, spinocerebellar ataxia types 2 and 3, Wilson's disease, Woodhouse-Sakati syndrome, methylmalonic aciduria, and X trisomy) and disabling dystonia underwent bilateral GPi DBS (bilateral thalamic Vim nucleus in 1 case). The primary outcome was the difference in the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) between baseline, 1 year and last available follow-up. Preoperative factors such as age at surgery, disease duration at surgery, proportion of life lived with dystonia and severity of dystonia were correlated to the primary outcome.

Eleven patients were operated between February 2003 and December 2013. Age and duration of disease at time of surgery were 30 ± 19 and 12.5 ± 15.7 years, respectively. DBS effects on dystonia severity were variable but overall marginally effective, with a mean improvement of 7.9% ($p = 0.39$) at 1-year follow-up and 16.7% ($p = 0.46$) at last follow-up (mean 47.3 ± 19.9 months after surgery). No preoperative factors were identified to predict the surgical outcome.

Our findings support the current knowledge that DBS is modestly effective in treating rare inherited dystonias with a combined phenotype. However, the BFMDRS might not be the best tool to measure outcome in these severely affected patients [1)].

Case report

Paucar et al., from the Karolinska University Hospital, reported a 41-year-old Lithuanian woman, born to non-consanguineous parents, who was affected by a complex movement disorder starting at age 1.5 years. The patient obtained a university degree in education but worked as a librarian from age 28 to 32 retiring due to debilitating dystonia. Despite previous extensive work up at different centers no diagnosis was reached. Two maternal aunts were affected by solid tumors (breast and gastric cancer) and a paternal uncle died of leukemia. At onset her gait was described as unsteady and the patient was prone to falls. At age 16y the patient presented with craniocervical dystonia and dysarthria; dystonia progressed, becoming generalized. Prior testing for TOR1A, THAP1, TH, and GCH1, and Huntington's disease was negative; Wilson's disease was also ruled out. The patient was ex- amined at our center at age 35 and went through neuroimaging, la- boratory and genetic analyses as well as neurophysiological tests. Oral and written consent was obtained for this report. The patient never underwent spinal surgery. Upon examination the patient displayed disabling camptocormia that resolved when the patient lay down or leaned against a wall. She squatted as a sensory trick to reduce the camptocormia magnified during ambulation (“duck walk”; Video). Movements also induced or exacerbated blepharospasm, leg posturing, and retrocollis. There were no telangiectasias or obvious signs of ataxia or oculomotor abnormalities, but broad-base gait during childhood was documented in her medical records. There was no evidence of either recurrent infections or pulmonary symptoms. EMG displayed neuro- genic abnormalities but MRI of the spinal cord was normal. Laboratory analyses revealed elevated AFP (75 µg/l, normal value < 8) but https://doi.org/10.1016/j.parkreldis.2018.12.017 normal Ig levels and normal karyotype. Sequencing and multiplex li- gation-dependent probe amplification of SETX was normal ruling out ataxia with oculomotor apraxia type 2 (AOA2). Western blotting of a lysate of a lymphoblastoid cell line (LCL) made from the patient's blood demonstrated a very low level of ATM with low-level ATM kinase ac- tivity . Previously described mutations c.3214G > T; p.Glu1072Ter and c.8147T > C; p.Val2716Ala in ATM were then identified in her DNA. Together, the presence of these two ATM mutations and low level ATM kinase signaling confirmed the diagnosis of vA-T.

Supplementary video related to this article can be found at https://doi.org/10.1016/j.parkreldis.2018.12.017.

Several unsuccessful pharmacological attempts to treat her dystonia were made over the years. Treatment with DBS was proposed but the patient declined due to the poor outcome reported for a patient with dystonia associated with vA-T [2].

1)
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2)
Paucar M, Schechtmann G, Taylor AM, Svenningsson P. Variant ataxia-telangiectasia with prominent camptocormia. Parkinsonism Relat Disord. 2018 Dec 17. pii: S1353-8020(18)30551-0. doi: 10.1016/j.parkreldis.2018.12.017. [Epub ahead of print] PubMed PMID: 30579816.