Ataxia-Telangiectasia Presenting as Cerebral Palsy and Recurrent Wheezing: A Case Report

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Patient: Male, 8

Final Diagnosis: Ataxia-telangiectasia

Symptoms: Ataxia • sinopulmonary infection • telangiectasiae • wheezing

Medication: —

Clinical Procedure: IVIG supstitution

Specialty: Pediatrics and Neonatology

Objective: Rare disease

Background: Ataxia-telangiectasia (A-T) is an autosomal recessive disease that consists of progressive cerebellar ataxia, variable immunodeficiency, sinopulmonary infections, oculocutaneous telangiectasia, radiosensitivity, early aging, and increased incidence of cancer.

Case Report: We report the case of an 8-year-old boy affected by A-T. At 12 months of age, he had a waddling gait, with his upper body leaning forward. Dystonic/dyskinetic cerebral palsy was diagnosed at the age of 3 years. At age 6 he was diagnosed with asthma based on recurrent wheezing episodes. A-T was confirmed at the age 8 years on the basis of clinical signs and laboratory findings (increased alpha fetoprotein - AFP, immunodeficiency, undetectable ataxia-telangiectasia mutated (ATM) protein on immunoblotting, and identification A-T mutation, 5932G>T).

Conclusions: The clinical and immunological presentation of ataxia-telangiectasia (A-T) is very heterogeneous and diagnostically challenging, especially at an early age, leading to frequent misdiagnosis.

MeSH Keywords: Ataxia Telangiectasia • Cerebral Palsy • Gastroesophageal Reflux • Respiratory Sounds

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Background

Ataxia-telangiectasia (A-T) is an autosomal recessive disease that consists of progressive cerebellar ataxia, variable immunodeficiency, sinopulmonary infections, oculocutaneous telangiectasia, radiosensitivity, early ageing, and increased incidence of cancer [1,2]. This disease is often misdiagnosed in early childhood, before the development of a full clinical picture. Considering that in most of the cases the first signs of the disease are movement disorders of varying severity, the most common misdiagnosis is cerebral palsy [3]. We report the case of an 8-year-old boy with A-T confirmed by immunoblotting and genetic tests.

Case Report

An 8-year-old boy was referred to the pediatric allergy and pulmonology department for frequent sinopulmonary infections and recurrent wheezing.

He was the third child of non-consanguineous parents, with 2 older, healthy sisters. Previous medical history revealed intrauterine growth retardation (IUGR) in the 7th month of pregnancy. When he started walking, his mother noticed a waddling gait, with his upper torso leaning forward. At the age of 3, he was hospitalized and diagnosed with dystonic/dyskinetic cerebral palsy by a neuropediatrician.

When he was 6 months old, he had the first wheezing episode, which was treated with short-acting beta-agonists (SABA) and systemic corticosteroids. A period free from respiratory disorders ensued until the age of 6, when he started to develop recurrent bacterial and viral (not opportunistic agents) respiratory infections (ear infections and sinusitis) and recurrent wheezing.

On presentation, at the age of 8, the patient’s general condition was good, and he was afebrile with normal vital signs. Body weight was 24 kg (15th percentile) and height was 125 cm (5th percentile). Telangiectasias had been present on the skin of the upper part of the back, between the scapulae, on the face, neck and on the sclerae of both eyes (Figure 1). Neurological examination revealed a wide-based gait, walking on heels and toes was clumsy, with the upper part of his body leaning forward. Deep tendon reflexes were diminished, and the Babinski sign was positive. Finger-to-nose test showed dysmetria, and dysdiadochokinesia and choreoathetosis were also present. He was dysarthric, and cognitive function and IQ were normal.

Chest radiography showed a small thymic shadow, decreased mediastinal lymphoid tissue, and peribronchial infiltrates. Twenty-four-hour esophageal pH monitoring showed pathological gastro-oesophageal reflux (171 reflux episodes, 6 lasting longer than 5 min, reflux index 11.4%). Lung function measurements were in the normal range but with positive bronchodilatory test. Due to a history of cryptorchism and orchiopexy, an ultrasonography scan of the testicle had been performed, which revealed diffuse microthiasis involving the right testicle. MRI scan of the brain demonstrated cerebellar atrophy (Figure 2). Immunological work-up revealed hypogammaglobulinemia, low absolute count of T-cells, T-helper and B-lymphocytes, and low T-lymphocyte proliferation in the presence of mitogens (Table 1). Alpha-fetoprotein (AFP) was 425.5 μg/L (reference range<15 μg/L) and immunoblotting showed no cellular ataxia-telangiectasia mutated (ATM) protein (Figure 3). Only 1 ATM mutation was found – a Polish/Eastern European mutation, 5932G>T. We are still looking for the second one.

The treatment plan for the patient included intravenous immunoglobulin (IVIG) substitution (400 mg/kg every month),
pantoprazole 20 mg/day, anti-asthma therapy together with respiratory physical therapy, and aggressive antibiotic treatment as indicated. Physical therapy was also necessary to maintain the locomotor system. Contrast studies were avoided. Regular oncological control was also arranged. The patient has been infection-free during the follow-up period extending now to 18 months. His respiratory function has been improved according to spirometry findings.

Table 1. Immunological status.

|                      | Normal range          |
|----------------------|-----------------------|
| WBC                  | 7.05×10⁹/l            |
|                       | 4.4–11.6×10⁹/l        |
| neu                  | 58%                   |
|                      | 34–69%                |
| ly                   | 31%                   |
|                      | 19–52%                |
| mo                   | 8%                    |
|                      | 5–15                  |
| eo                   | 3%                    |
|                      | 0–9%                  |
| IgG                  | 0.2 g/l               |
|                      | 6.3–15.8 g/l          |
| IgG1                 | <0.19 g/l             |
|                      | 3.69–11.1 g/l         |
| IgG2                 | <0.36 g/l             |
|                      | 0.75–3.95 g/l         |
| IgA                  | 0.01 g/l              |
|                      | 0.4–2.51 g/l          |
| IgM                  | 2.16 g/l              |
|                      | 0.47.275 g/l          |
| Total IgE            | 11.6 kU/l             |
|                      | <7.6 kU/l             |
| CD3                  | 69% (1078/μl)         |
|                      | 54–80% (1320–3300/μl) |
| CD3+CD4+             | 34% (531/μl)          |
|                      | 25–46% (620–2400/μl)  |
| CD3+CD8              | 30% (469/μl)          |
|                      | 15–42% (390–1100/μl)  |
| CD19                 | 15% (234/μl)          |
|                      | 9–37% (270–2050/μl)   |
| CD3-CD16+56+         | 17% (266/μl)          |
|                      | 5–20% (190–740/μl)    |
| CD3-CD16+56+         | 17% (266/μl)          |
|                      | 5–20% (190–740/μl)    |
| Antitetanus antibody by ELISA | 1 IU/ml |
|                      | 0.01–0.15 IU/ml       |
| Isohaemagglutinins   | B Rh+, anti-A IgM 64 (score 59), anti-A IgG 32 (score 51) |
|                      | Anti-A Ig M ≥1:8      |
| T-lymphocyte proliferation test | Mitogens: |
|                       | PHA 8.3% S phase      |
|                       | 17–39%                |
|                       | Con A 3.1% S phase    |
|                       | 7–18%                 |
|                       | PWM 10.3% S phase     |
|                       | 9–25%                 |

CD – cluster of differentiation; Con A – concanavalin A; ELISA – enzyme-linked immunosorbent assay; eo – eosinophils; Ig – immunoglobulin; PHA – phytohemagglutinin; ly – lymphocytes; mo – monocytes; neu – neutrophils; PWM – pokeweed; Rh – rhesus; WBC – white blood cells.

Figure 3. Western blot of nuclear extracts from lymphoblastoid cell lines. Our Croatian patient lacks ATM protein. Aprataxin was used as a loading control.
**Discussion**

We present the case of an 8-year-old boy with A-T who was initially diagnosed with cerebral palsy and asthma (recurrent wheezing episodes) at an early age. At the age of 8, when he developed oculocutaneous telangiectasia, clinical diagnosis of A-T was obvious. However, the diagnosis was delayed, probably due to the rarity of the disease and the low awareness of it in our medical population.

A-T is a complex multisystem disorder with an estimated incidence of 20,000 to 100,000 live births [4]. The overall risk of cancer mortality in ataxia-telangiectasia is 100 times higher than that of the general population, and approximately 10–25% of all patients with A-T will develop malignancy [5,6]. The frequency of ATM allele heterozygosity is estimated to be 1.4–2%. Although A-T is a recessive disease, it is interesting to note that ATM heterozygotes die on average 7–8 years earlier than non-carriers, mostly from ischemic heart disease or cancer, suggesting prevalence/dominance of the defective gene [7,8].

The disease is caused by a mutation in the ATM gene, found on chromosome 11q22-23. It is a member of a family of phosphatidylinositol-3-kinase – related genes [9]. The gene encodes the protein kinase ATM, which is the key early regulator of DNA damage response. ATM protein is expressed mainly in the nucleus of lymphocytes, fibroblasts, and germ cells [10]. It is also found in the cytoplasm of neurons, where it monitors oxidation states [11]. More than 400 mutations in the ATM gene have been described in A-T patients, making the mutation detection expensive and impractical in everyday practice [12]. Most patients (90%) present a classic form of A-T resulting from the presence of 2 mutations, leading to total loss of the ATM protein. Most A-T patients carry unique mutations [13].

Until now, we have found only 1 ATM mutation in our patient, which could suggest that he has a compound heterozygote for 2 different ATM mutations.

An abnormal sensitivity of A-T cells to X-rays and certain radiomimetic chemicals leads to chromosome and chromatid breaks. Acquired nonrandom chromosome rearrangements especially affect lymphocytes chromosome at 7q and 14q that are involved in T-cell receptors and heavy-chain immunoglobulin coding and in the development of hematologic malignancies [14,15]. A-T patients are at high risk of having impaired responses to infection with pneumococci, which may be a cause of recurrent sinopulmonary infections in these patients [16,17]. Authors from Brazil analyzed the production of antibodies to polysaccharide antigens in patients with A-T and found that the levels of immunoglobulin G (IgG) antibodies to serotypes 1, 3, 5, 6B, 9V, and 14 of *Streptococcus pneumoniae* before and after immunization with 23-valent polysaccharide vaccine were significantly lower than in the healthy population. In our case, immunodeficiency was not suspected. Reversible airway obstruction in A-T children is not rare [18]. With our patient, recurrent wheezing episodes were probably in part induced by viral infections, chronic aspiration, and pathological gastro-oesophageal reflux.

Ataxia is usually the first diagnostic hallmark of A-T, noticed in the first years of life. Oculocutaneous telangiectasias are the second most common major clinical manifestation of the disease, having its onset after the age of 3-6 years [14]. Since neurological impairment (ataxia) is a first symptom at an early age, the misdiagnosis of cerebral palsy is commonly found in 60% patients, as it was with our patient. Furthermore, IUUGR was probably the confusing factor in making the misdiagnosis of cerebral palsy, considering different teratogens (co-natal infections or medications) can cause IUUGR as well as cerebral palsy. Cerebral palsy is a heterogeneous group of nonprogressive clinical syndromes characterized by motor and postural dysfunction that occurred in the developing fetal or infant brain. It is particularly important to determine whether the condition is static rather than progressive or degenerative [19]. The neurological symptoms in A-T are progressive and most patients will be wheelchair-bound by the time they reach their teens. They also develop progressive dysphagia with aspiration due to decreased cough reflex, or silent aspiration [20]. Therefore, our case shows that serum AFP testing should be a routine part of the diagnostic workup of any child with persistent ataxia. Why individuals with A-T have elevated levels of AFP is not yet known. The profile of AFP species in A-T patients is similar to those seen in neonates and patients with chronic hepatitis, suggesting a hepatic origin for the elevated AFP in A-T patients. It is proposed that the AFP gene in the A-T liver could be under aberrant transcriptional control, perhaps secondary to a defect of DNA regulatory proteins, which are necessary for hepatic maturation [21].

A-T patients usually die in their teens or early 20s. Median survival in 2 large cohorts, 1 prospective and 1 retrospective, was 25 and 19 years, with a wide range. Mortality is mainly caused by cancer, a high rate of pulmonary failure, and a compromised immune system, which causes recurrent respiratory infections [22]. Leukemias and lymphomas are the most common cancers in A-T children, whereas solid tumors are more frequent in adults [14]. Testicular microlithiasis, which we found in our patient, might be indicative for A-T, as it is a condition associated with coexistence or future development of testicular neoplasms [23,24].

In addition, there are several laboratory tests that can be used to support a clinical diagnosis of A-T. Karyotyping of lymphocytes reveals characteristic chromosomal aberrations, including telomeric fusion, increased rate of telomeric shortening, and translocations such as t (7;14) [11]. After the age of 6–8
years, MRI shows cerebellar atrophy most prominent in the region of the vermis, with prominent folia and increased surrounding cerebrospinal spaces. Performed at any age, Western blotting of nuclear lysates, also known as immunoblotting, allows a semi-quantitative assessment of ATM protein level; 95% of ataxia-telangiectasia cases lack this protein and the test itself has better than 98% sensitivity and specificity [25]. The colony survival assay is a test for radiosensitivity and is abnormal in approximately 93% of A-T cases [26]. Genetic testing for mutated ATM gene is the “gold standard”, but due to the size of the gene and hazards of interpreting many DNA sequence variation, it is not the recommended approach for diagnosis. ATM mutation 5932G>T has been found at low levels in many European studies [13,27] and is a founder mutation among Polish and Russian A-T families [13,28].

At present there is no therapy available to cure or prevent the progression of A-T; therefore, treatment is symptomatic and supportive. As with the other disorders accompanied by hypogammaglobulinemia, frequent infections can be treated with IVIG replacement. Patients with recurrent lower respiratory tract infections should be assessed for dysfunctional swallowing and aspiration, choosing diagnostic procedures without exposure to radiation and contrast media [12]. The use of conjugated pneumococcal vaccine might be beneficial, considering the high frequency of infections with S. pneumoniae. Frequent follow-up for respiratory function and physical therapy is also recommended [20]. Modest improvements can sometimes be achieved by treating the associated neurological symptoms of A-T [29]. Basal ganglia dysfunction may respond to L-DOPA derivatives, dopamine agonists, and anticholinergics. Amantadine, fluoxetine, or buspirone can improve speech and coordination. Tremors are often controlled with gabapentin, clonazepam, or propranolol. A recent case report illustrates a long-known fact that steroids produce a short-term improvement in ataxia [30]. There is no cure for the progressive neurodegeneration, but some hope can be found in the use of antioxidants and mutation-targeted therapy [1].

**Conclusions**

Early diagnosis improves survival and quality of life in patients with A-T by limitation of ionizing radiation, IVIG substitution, antibiotic therapy and vaccination, frequent onological follow-up, and respiratory physical therapy. Regular lung function measurements and anti-reflux and anti-asthma therapy can improve lung function and prognosis of A-T patients. The discovery of the ATM gene could help recognize and perhaps reduce heterozygote mortality in the future when the costs of genetic testing become less expensive and time-consuming.

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