

**Case Report****THE COMPLEXITY OF EARLY DIAGNOSIS OF CONGENITAL ATAXIA: A CASE REPORT**Olena Koreniuk<sup>1\*</sup>, Svitlana Ilchenko<sup>1</sup>, Anne P. Hernandez<sup>2</sup>

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**Abstract:** Ataxia-telangiectasia (AT) is a rare form of phakomatoses with multisystem lesions that are characterized by a specific neuro-cutaneous syndrome. It is a multisystem disease that includes progressive clinical manifestations of cerebral ataxia, oculocutaneous telangiectasia, and increased susceptibility to cancer due to ionizing radiation sensitivity. Lack of awareness of this disease by medical providers could ultimately lead to a delay in diagnosis and increase morbidity in patients. This case study presents the history of a female adolescent patient with AT, who was eventually placed in protective custody. She was clinically observed for fifteen years. This paper demonstrates the complexity of early diagnosis of AT in children. The importance of a comprehensive evaluation of neural and immunological systems, timely genetic testing, and aggressive treatment of infectious diseases is paramount in the formulation of an appropriate treatment plan. Early diagnosis and management significantly improve the prognosis and quality of life for these patients.

**Keywords:** congenital ataxia, telangiectasia, children, the complexity of diagnosis

**INTRODUCTION** Congenital ataxia is a clinically and genetically heterogeneous group of progressive neurodegenerative disorders. The main clinical characteristic of ataxias is movement and coordination imbalances caused by degeneration of the corresponding afferent and efferent neurons. Hereditary ataxias are among the most difficult clinical neurology and neurogenetic diagnoses and have been a focal point of interest in neurology [1]. The clinical phenotypes of congenital ataxias range from isolated cerebellar dysfunctions to severe multisystem syndromes; one example of this would be ataxia-telangiectasia (AT) [2].

AT is a rare form of phakomatoses with a specific neuro-cutaneous syndrome. It is an autosomal recessive, multisystem disease characterized by progressive cerebellar ataxia, telangiectasia of the eyes and skin, variable immunodeficiency with a predisposition to sinopulmonary infections [3]. The incidence of this

pathology is one case per 40,000-100,000 live births. There are no racial differences in the disease structure, and based on the inheritance type, it equally impacts both genders [4].

Congenital ataxia-telangiectasia (also known as Louis-Bar syndrome) is associated with mutations in the ATM gene (ataxia telangiectasia mutated), the main function of which is to repair DNA breaks and maintain the integrity of the genome in the cell. AT is a result of genome instability or DNA damage response syndrome [5]. The ATM gene is located in the long arm of the 11 chromosomes in the 11q22-q23 region [6,7,8]. It is assumed that vascular abnormalities may cause thymus hypoplasia and changes in the nervous system due to a mesodermal defect or autoimmune reactions to an antigen common to thymocytes and nerve cells. However, a causal relationship between immune, vascular, and neurological systems has not yet been proven [9,10]. The genome instability at the chromosomal level is the genetic cause of ataxia and other neurological presentations.

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Regular and mosaic forms of chromosomal diseases always negatively affect the brain's functions and manifest themselves in the various forms of cognitive delay, autism, and epilepsy [11,12]. AT is characterized by degenerative changes in cerebellar tissues with progressive death of Purkinje cells. The degenerative changes can also affect other structures in the brain. Computerized tomography and magnetic resonance imaging (CT and MRI) usually determine the amount of atrophy of the vermis and cerebellar hemispheres with the expansion of the cerebrospinal fluid [13,14]. Structural neuroimaging may be absent in the early stages of the disease, but it becomes more noticeable with age [12].

AT's initial manifestation is usually neurological, as evidenced by symptoms of cerebellar ataxia with gait disturbance, tremors of the head and trunk, choreoathetosis, intentional tremors and oculomotor disorders. There is a progressive neurological disability in these patients. At 2-6 years of age, the asymmetric telangiectasias appear on the skin and mucous membranes, disrupting skin pigmentation. The disease is characterized by hereditary angiopathy with the initial occurrence of ocular telangiectasias. Spider veins have appeared on some patients' eyelids' skin, nose, face, neck, and extremities [15].

AT is also characterized by combined immunodeficiency, which makes patients prone to frequent infectious, formation of chronic bronchopulmonary processes, and oncological diseases. The serum immunoglobulin A is substantially reduced or absent. The patients have a different degree of suppression of IgG, IgM, and IgE [6,8,15]. In addition, AT patients have low blood levels of  $\alpha$ -fetoprotein, lymphopenia, and eosinophilia. The cytogenetic study of lymphocytes shows chromosomal instability, which leads to increase sensitivity to ionizing radiation. These patients could also have aplasia or hypoplasia of the thymus, lymph nodes, and the spleen [15,16].

The clinical symptoms of congenital ataxia and delayed psychomotor development requires differentiating this diagnosis from infantile cerebral palsy, congenital malformations of the central nervous system, and other forms of hereditary ataxias. Without a pediatric genetic consultation, the diagnosis of AT can be delayed. The combination of ataxia and telangiectasia with recurrent respiratory diseases can cause significant difficulties and confusion in diagnosing this rare syndrome.

**CASE PRESENTATION** Patient K., a 15 years-old girl, **was** followed in a pediatric department since she was two months of age. She had been repeatedly treated for respiratory diseases and other health issues. The girl was a product of a 2<sup>nd</sup> pregnancy, and the 2<sup>nd</sup> live-born child, Apgar scores corresponded to 7 at the first minute after birth and 8 points at the five-minute interval. The baby's weight at birth was 3400 g and length 51cm. During the 2<sup>nd</sup> month of life, she was switched to commercial formula. Her psychomotor and physical development, in the first seven months, were within the normal range. Specifically, she achieved the following milestones: at three months, the child could hold her head up; at five months, she turned from the abdomen to the back, and she started sitting by herself at seven months. However, her crawling skills were delayed until one year of age, and she was not able to walk until she reached two and a half years and only than with assistance. Speech development was significantly delayed, and she was not able to verbalize single words until the age of two. This was attributed to the fact that the child grew up in a dysfunctional family where the parents' abused alcohol. Initially her physicians thought that her global developmental delays and frequent infectious illnesses were due to parental neglect. The child also was diagnosed with chronic bronchitis, pyelonephritis, and hypochromic anemia of moderate severity. Since birth, the girl had repeatedly suffered from acute respiratory infections, bronchitis, impetigo, and enterocolitis. She had sepsis at the age of two, bilateral bronchopneumonia, bilateral acute otitis media, and hepatitis.

At the age of three, the patient was diagnosed with cerebral palsy and ataxia. She had progressively developed difficulties in muscular coordination of the head and extremities with trunk swaying, gait ataxia, dysnergia, muscular hypotonia, and history of frequent falls. She also suffered from dysarthria. Recurrent impetigo was noted, and she presented with a "stellate" rash, which was later diagnosed as telangiectasias. At the age of ten, seizure disorder was noted. Her pediatric neurologist diagnosed her with epilepsy in the form of complex absences and complex partial seizures. Pyelonephritis, acute vulvovaginitis, intestinal dysbiosis, and recurrent bronchitis were documented. At the age of 11, she was evaluated by a pediatric geneticist and diagnosed with Louis-Bar syndrome vs. leukodystrophy. An MRI of the brain was performed to distinguish between the two medical conditions and did not reveal pathological changes, which are generally observed in leukodystrophy.

However, the immunological study established lymphopenia, a significant decrease in IgA and IgE, which allowed us to diagnose Louis-Bar syndrome.

although her sensory examination was normal. She was able to sit down by herself but unable to stand without support. The patient could not ambulate (Figure 1) but



Figure 1. Picture of the 15 years-old girl with ataxia-telangiectasia syndrome



Figure 2. Picture drawn by the 15 years-old patient with ataxia-telangiectasia syndrome

From a psychological perspective, the child was placed in an orphanage for disabled children at the age of 10. She had a history of multiple hospitalizations due to recurrent infectious diseases and numerous other health problems. There was an increase in the frequency of epileptic seizures, and her psychological state was adversely affected. Dysfunction of the pelvic organs was manifested by enuresis.

**Objective Status:** On clinical examination, the patient was emotionally labile, inhibited, and could only answer simple questions. Severe dysarthria was noted, her voice was soft, and her vocabulary was limited to 10-12 words. It was also observed that she sometimes responded with gestures. The patient's cognitive function was reduced. Cognitive impairment was observed in her intellectual abilities. Physical development was significantly delayed. The patient's muscle tone was markedly reduced,

could eat independently. It was observed that she tired easily. She was able to write letters and draw figures, but with difficulty (Figure 2). Esotropia and nystagmus were noted. The patient exhibited excessive hypersalivation. She also had thoracic and lumbar scoliosis.

Her skin was pale, dry to the touch, with multiple telangiectasias on her face and neck. The vascular pattern on the patient's eyeballs was pronounced, and an injection of the sclera was observed. The peripheral lymph nodes were small, single up to 0.8–1.0 cm. in diameter. Hyperemia was manifested in the nasopharynx region. She presented with a rare and unproductive cough and mixed dyspnea. Pulmonary sounds to percussion were diminished over the bases of both lungs. Breath sounds were weakened bilaterally to auscultation with rhonchi; and rales were most prominently heard at the lower-left section of the lung. Blood tests revealed hypochromic

anemia, leukocytosis, neutrophilia and increased ESR. Urine analysis showed leukocyturia and proteinuria. A chest X-ray confirmed left-sided, lower lobe pneumonia with chronic bronchitis.

Ultrasound of the kidneys revealed heterogeneity of the pyelocaliceal system with a small hyperechoic lesion and some dilatation of the calyx on the left side. The complete metabolic panel revealed an elevation in blood urea, blood nitrogen, and creatinine levels. ECHO-encephalogram showed: moderate pulsation of lateral echo complexes without clear lateral features; signs of moderately increased intracranial pressure; and indication of hydrocephalic disorders - on the left; but no focal changes were detected. The performed immunological blood test revealed lymphopenia, increased CD8, CD16, CD19, low phagocytic activity, and a significant decrease of IgA level, up to 0.05 g/L.

Complex treatments and rehabilitation interventions alleviated symptoms of the pneumonia. There was an improvement in the child's health which led to a decrease in the frequency and severity of her seizures. An increase in motor activity and emotional tone was noted. Overall, there was an improvement in practical self-care skills and her quality of life.

**CONCLUSION** This case demonstrates the complexity of early diagnosis of ataxia-telangiectasia syndrome in children when other neurological disorders can also be present. Different variations of the disease's development may be present. For example, a late manifestation of pathognomonic skin syndrome can complicate the diagnosis of ataxia-telangiectasia syndrome, with various other forms of cerebellar ataxia.

The combination of neuro-dermal syndrome, with a positive history of varied, recurrent infectious diseases, should be enough to justify the necessity for genetic testing. Each case is unique, and the therapy should focus not only on treating neurological symptoms but also on preventing recurrent infectious diseases. As patients with AT mature, cancer screening should be mandatory. This treatment approach can greatly improve the patients' prognosis, their quality of life, and also life expectancy.

**Disclosure:**

The author declares no conflicts of interest.

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