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Ataxia Telangiectasia Presenting with Idiopathic Thrombocytopenic Purpura in a 4-Year-Old Boy

Sara I[1*], Ali Saeedi B[2], Arash A[3], Abolnezhadian F[4]

1Department of Immunology, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

2Department of Student Research Committee, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

3Department of Health Research institute, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

4Department of Pediatrics, Abuzar Children's Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

[*]**Corresponding author**: Sara Iranparast, Department of Immunology, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran, Tel: +989161811429; E-mail: Sara.Iranparast@yahoo.com

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Abstract

Ataxia Telangiectasia (AT) is autosomal recessive disorder, characterized by progressive neuro degeneration telangiectasia, immunodeficiency, cancer susceptibility, and some laboratory abnormalities. It is a rare immunodeficiency disease and AT disease is due to the mutation in the gene Ataxia-Telangiectasia Mutated located on chromosome. This study shows that finally the importance of the clinical case introduced is whether the mutation in gene expressing Ataxia-Telangiectasia Mutated can disrupt the complex mechanisms of central and peripheral tolerance of immune system.

Keywords: Ataxia telangiectasia; Immunodeficiency; Cancer susceptibility; Live births

Introduction

AT is a rare immunodeficiency disease with an estimated prevalence of one per 40,000 to one per 100,000 live births [1,2]. AT disease is due to mutation in the gene ATM [Ataxia-Telangiectasia Mutated] located on chromosome [3], which encodes the protein that plays a role in detecting the region of back down in DNA, stopping the process of making a detective DNA, and recruiting other proteins involved in DNA repair. The clinical manifestations of AT, are usually presented at the first 4-5 years of life. Both ataxia and telangiectasia are hallmarks of AT disease [1]. Ataxia is evidenced in AT patients at an early age in unbalanced movements and wobble when walking and event standing, which can be attributed to a defect in the cerebral region of the brain [4]. Another characteristic of AT disease is telangiectasia, small dilated blood vessels, which causes a blood shot in the sclera and sun exposed areas of skin. Telangiectasia is also manifested at the age of 5-6 years not in infancy. Other features of at patients include delayed growth, predisposition to infections and cancers, which occur due to immune system disorders [5-7]. Also, other neurologic disorders, which may be confusing, should be considered when diagnosing AT. Typically, laboratory tests such as sequencing is performed to confirm diagnosis of AT. ITP is a type of thrombocytopenic purpura that is associated with immune system related degeneration of the platelets, and has been shown to inhibit the differentiation of platelets from megakaryocytes, which can be one of the reasons for the contraction of platelets, while the bone marrow of these patients is normal [8]. Nearly 60 percent of cases, antibodies against platelets are detectable [9] which Most of them are of the immunoglobulin G (IgG) type, which are made against platelet membrane antigens, such as glycoproteins IIb-IIIa or Ib-IX. [10] The stimulus for auto-antibody production in ITP is presumably abnormal T cell activity [11-13]. Covering platelets with IgG make them susceptible to opsonization and phagocytosis by splenic and liver macrophages. The IgG autoantibodies can also damage megakaryocytes. In addition, impaired production of thrombopoietin, which is the stimulant for platelet production, may be a contributing factor to a decline in circulating platelets [14].The simultaneous occurrence of immunodeficiency (AT) along with an auto-immune disorder (ITP) is an interesting topic that has been addressed in this study.

Investigation

Transient leukopenia (3100, 3800/mm^3; normal values (NV) [4,000–10,000/mm^3] was associated with increased ESR and 3+CRP in this case; also a moderate anemia (mild decrease in RBC count (3.97×10^6/µl) Normal Values (NV) [4.5–6.3×10^6/µl), HGB 7.7–10.8 g/dl, HCT: 29.6-33.4%) was observed. The number of MCV, MCH, and MCHC were also reduced in this patient. Despite the fact that water PT and PTT were normal, the number of platelets declined sharply, (45.4/µl normal values (NV) [130-400b×10^3/µl]). After all, the serum cautions level, including sodium, potassium, and Crum, as well as uric acid and BUN, were normal in this patient. Platelet counts were severely decreased (PLT: 45.4/mm3; NV [150-410/mm^3]). Neutrophil function test was done. The result of DHR test has been reported 144, which show normal phagocyte function of neutrophils. The result of hepatic enzymes were normal, but in the case of cardiac enzymes, a temporary decrease in ALP and an unstable increase in AST (up to 51U/L; NV[up to 37 U/L]) and LDH (793 U/L; NV[100-500 U/L] were observed in this patient. The assessment of serum antibodies also showed that the IgG level was normal (550 mg/dl, NV: 20-205 mg/dl), but the serum IgA rate was sharply reduced (less than 10 NV: 20-205mg/dl). The patient underwent Whole Exmore Sequencing (WES) for definite diagnosis. A novel mutation in ATM gene (NM_000051: exon7: c.C664T: p.Q22) was found that leads to home stop again mutation which can cause protein dysfunction. WES sequence in the present study was performed by Illumine high throughput DNA sequencing technology and the values were

compared to standard references and parental WES and mutations were interpreted by board certified laboratory clinicians in accordance with clinical findings.

Clinical History

The patient is a 4-year-old boy with a body weight of 13 Kg who referred to the center for Allergy and Immune Deficiency in Abuzar Hospital in Ahvaz, with a complaint of fever, cough, and shortness of breath. This patient had a history of several hospitalizations due to frequent ITP. However, there is no history of a specific illness in his family. At the time of the admission, the patient was ill, but no toxic symptoms were reported to him. He had repeated coughs from the past 3 days, as well as fever and shortness of breath in the last 12 days. Despite his oxygen saturation of 92%, he was diagnosed with pneumonia as proven by chest x-ray. According to the doctor's request, an ultrasound was performed. The results of which showed that kidney and bladder was normal, and abdominal and pelvic ultrasound also showed a mild fluid. There was no evidence of pleural effusion in bilateral pleural ultrasound. In addition, brain CT was normal (Figure 1).

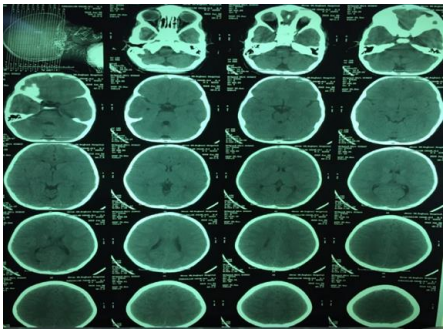

Figure 1: The result of brain CT scan, which shows it, is in a normal situation

And there was no trace of edema and cyanosis. Also, the eyes were examined and the abnormal blood vessels in the eyes were observed in the form of telangiectasia (Figure 2).

Figure 2: This picture shows the telangiectasia trace in the patient's eye, which is evidenced in the form of small dilated blood vessels

Discussion

Ataxia Telangiectasia (AT) is known as Multisystem Disorders with Immunodeficiency that has a range of symptoms mentioned in the introduction along with a variety of Immunodeficiency's. According to reports, in 70% of AT cases, there are evidences of immunodeficiency. In this part, we will review the most important immunodeficiency disorders identified in AT patients. So far the most common humeral immune deficiency reported in these patients is a defect in IgA and IgG2 production, probably due to the role of the ATM in class switching of antibody T cell in the cell body deficiency with thymus hypoplasia has also been reported in some cases. Defect in the production of antibody against polysaccharide antigens are also another characteristics of some AT patients. An increased risk of breast cancer as well as some types of leukemia has been observed in some of these patients, which is unclear because of a defective in DNA repairing system, or due to defect in antitumor defense, or both of them, responsible for this relation. In cases of AT, especially in children, insulin-resistant diabetes mellitus has been reported. Idiopathic thrombocytopenia or Immune Thrombocytopenic Purpura (ITP) is a type of acquired primary thrombocytopenia, which is one of the most common thrombocytopenic agents. Generally, secondary ITP is caused by Hepatitis C Virus [HCV], Systemic Lupus Erythematosus [SLE], and Chronic Lymphocytic Leukemia [CLL] or as a result of drugs that there is no indication in the case of the present case of a specific type of secondary ITP. This can confirm the idea that the gene mutation associated with ataxia telangiectasia and the production of a specific type of ATM protein, which plays a key role in regulating the function of cells, has led to this severe ITP. The simultaneous occurrence of immunodeficiency along with a number of autoimmune disorders (a form of immune system hyperactivity), seemingly contradictory, have recently been of great interest in a comprehensive set of studies in the paper published in the journal of Rheumatology nature review. In fact, autoimmunity and immunodeficiency can be considered as two sides of a coin, so further studies are needed to achieve a better perception of this issue. But unlike some of the other primary immunodeficiencies, AT has not yet been propounded as a PID that occurs at the same time as an autoimmune disorder. In other words, the relationship between ITP and primary or secondary immunity defects is not well defined. Among the studies conducted in this field, only a Case Report article was published by researchers in North Carolina in 2010, but different aspects of the case presented at Ahwaz Children's hospital varies from different aspects. the patient was a seven year old boy who was known as an oculocutaneous-telangiectasia in the early years of his life due to obvious symptoms of dermatological and neurological disorders. Due to lymphopenia and hypogammaglobinemia, he has undergone IVIG treatment and a regular regime for three years, described in the related article. During this course of treatment, sudden symptoms of ITP appeared in the patient. In the case, however, the injection of 1 g/Kg of IVIG effectively increased platelet counts, which had been severely reduced before the onset of the treatment process, indicating ITP in this patient. Eventually, after two weeks of administration of IVIG, petechial skin manifestations improved, and platelet count was normal (454 K/m3). As indicated in the introduction of the present case, the symptoms of ITP have been observed in a 4 year old boy who has been diagnosed with AT during his hospitalization at Abuzar Hospital, while the patient has not treated with IVIG for a long and regular period. The other difference between these two case report studies is related to the type of mutations detected. The mutation of 3245delATCinsTGATwas reported in the case report published in 2010, while in the present

survey, novel mutation (NM_000051: exon7: c.C664T: p.Q22) was found that leads to 11 home stop gain mutation which gene ATM in, and it can cause protein dysfunction. Therefore, as mentioned at the beginning of the discussion; the coincidence of autoimmunity and the defects of the immune system have been one of the most attractive challenges for clinical immunologists. Nowadays, according to our findings from the immune system, the immunological contradiction between these two associated diseases is justified for various reasons, which we will mention in some of the following The occurrence of hypomorphic mutation in the gene involved in the somatic recombinant mechanism of T lymphocyte receptors, such as RAG1.2 and Arthemis, disrupts the differentiation of regulatory lymphocytes, which ultimately causes a primary immunodeficiency. Another justification for this issue is that one of the main indicators of immunodeficiency is the incidence of recurrent infections. Based on this hypothesis, recurrent infection is a permanent source for PAPMs, which by binding to the TLRs present on the surface of the Antigen Presenting Cell (APC), causes the stimulation and maturity of APCAs a result, APC provides the antigen to T lymphocyte, whereas due to a higher expression of the co-stimulatory, such as B7, it has a greater potential for antigen presenting, and it will provide the conditions for the development of potentially dangerous auto-reactive lymphocytes. Finally, the importance of the clinical case introduced is whether the mutation in gene expressing ATM can disrupt the complex mechanisms of central and peripheral tolerance of immune system If the response is yes, what could be the possible role of ATM in preventing autoimmune disorders? Further studies in humans and animal model with AT, especially with a special look at the novel mutation reported in current case report, can determine if Ataxia Telangiectasia, at least in certain cases, increases the susceptibility to autoimmunity.

Conclusion

This study shows that finally the importance of the clinical case introduced is whether the mutation in gene expressing ATM can disrupt the complex mechanisms of central and peripheral tolerance of immune system If the response is yes, what could be the possible role of ATM in preventing autoimmune disorders Further studies in humans and animal model with AT, especially with a special look at the novel mutation reported in current case report, can determine if Ataxia Telangiectasia, at least in certain cases, increases the susceptibility to autoimmunity

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