Ataxia-telangiectasia (AT) is a multisystemic, autosomal recessive inherited disorder. Patients with AT are characterized by a neurodegenerative course and combined immune deficiency. Immune impairments include T- and B-cell lymphopenia, as well as various humoral defects, such as hypogammaglobulinemia, decreased immunoglobulin G subclasses, and increased IgM levels.1,2

Pathogenic variants in AT are found in the ataxia-telangiectasia mutated (ATM) gene. ATM holds key functions in the DNA repair system and was previously shown to play a role in cell response to oxidative stress.1 One suggested mechanism for immune deficiency in AT consists of quantitative or qualitative defects in ATM, which result in accumulation of reactive oxygen species, followed by increased T-cell apoptosis on activation and proliferation.3

The newborn screening program for severe combined immunodeficiencies (NBS-SCID) is currently being implemented worldwide and has opened a doorway into a new era in the field of primary immune deficiencies (PID). Measurements of T-cell receptor excision circles (TREC) from dried blood spots enable prompt diagnoses and hematopoietic stem cell transplantations (HSCT) for patients with SCID. Consequently, morbidity and mortality rates of HSCT in SCID have been reduced.4

Interestingly, NBS-SCID was also found to be useful for non-SCID PID characterized by lymphopenia, such as AT.5 Mallot et al reported 7 of 13 patients with AT having low TREC copy numbers and CD4+ lymphopenia. Another study analyzing TREC results of 108 patients with different PID found that 5 of 6 patients with AT had low TREC copy numbers.5 Whole exome sequencing (WES) is thought to be complementary to TREC analysis, as was previously demonstrated in 4 patients with AT diagnosed in the Ontario NBS-SCID program. However, diagnostic difficulties concerning novel AT variants warrant further confirmation of their immune pathogenicity with functional assays.

In this issue of Journal of Allergy and Clinical Immunology: In Practice, Barmettler et al reported 3 infants with AT diagnosed with abnormal TREC numbers. Genetic workup revealed that all patients had pathogenic variants of ATM. The authors then used flow cytometry to analyze DNA repair–associated proteins in T, B, and natural killer cells including phosphorylated ATM, SMC1, and γH2AX. Samples were subjected to 2 Gy irradiation, which revealed intrinsic defects in DNA repair. This study stresses the importance of using immune functional assays to link phenotype and genotype features of patients with AT, particularly in those who were identified by the NBS-SCID assay. The 5-year experience of the Ontario NBS-SCID program is similar and showed confirmation of neonatal screening of AT by WES and mutagenesis sensitivity assays.

Early diagnosis of AT is important with regard to the immune system. Chronic sinopulmonary infections can be found in immune-deficient patients with AT and are associated with increased morbidity.5 Moreover, recent studies demonstrated dysbiosis of the upper airway in these patients and increased numbers of Streptococcus pneumoniae.6 Thus, antibiotic prophylaxis and close monitoring are warranted, especially in patients with AT with recurrent infections. Moreover, intravenous immunoglobulins should be administered to patients with AT with severe hypogammaglobulinemia and be considered in those with specific antibody deficiencies.7

Identifying patients with AT in early life can be challenging. Neurological deterioration usually manifests in toddler’s age.8 Misdiagnoses with other causes of ataxia, as well as phenotypic variability, can also delay the diagnosis. Increased alpha fetoprotein (AFP) is a laboratory clue and is known to be increased with age in patients with AT.9 However, AFP can also be elevated in non-AT inherited disorders with ataxia10 and its use as a biomarker in infants is limited.

Therefore, there is a need to adapt a neonatal screening methodology for AT. Indeed, the report of Barmettler et al in this issue further validates the use of NBS-SCID for AT diagnosis. First, newborns with abnormal TREC copy numbers on NBS-SCID, who do not meet SCID criteria, will be identified. Thereafter, combined genetic and immune workups are required to confirm the diagnosis. Immune functional assays of DNA repair, as presented by the authors, are essential in novel genetic variants and will confirm their pathogenicity in vitro.

In conclusion, applying this multilayer approach has the potential to promote diagnosis of AT in early life. Thus, physicians may offer better medical care and genetic counseling for the patients and their families. Further studies with larger cohorts of patients with AT are therefore needed.

---

1. Allergy and Clinical Immunology Unit, Department of Medicine, Hadassah-Hebrew University Medical Center, Jerusalem, Israel
2. The Lautenberg Center for Immunology and Cancer Research, Institute of Medical Research Israel-Canada, Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel

No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication August 16, 2020; accepted for publication August 19, 2020.
Corresponding author: Oded Shamriz, MD, Allergy and Clinical Immunology Unit, Hadassah-Hebrew University Medical Center, Ein Kerem, POB 12000, Kiryat Hadassah, 91120 Jerusalem, Israel. E-mail: oded.shamriz@mail.huji.ac.il.

2213-2198
© 2020 American Academy of Allergy, Asthma & Immunology
https://doi.org/10.1016/j.jaip.2020.08.040

---

**Editorial**

**Novel Approach for Screening and Early Diagnosis of Ataxia-Telangiectasias**

Oded Shamriz, MDa,b Jerusalem, Israel

---

---
REFERENCES


