

Clinical and therapeutic impact of newborn screening-based early detection of ataxia-telangiectasia

This study explores the critical role of newborn screening for inborn errors of immunity (IEI), in the early detection of IEI focusing on its ability to identify conditions beyond severe combined immunodeficiency (SCID) and the therapeutic implications. The study was approved by the pediatric Ethics Committee of Meyer Children's Hospital (ID number: 111/2023 "NBSxIEIs study").

A female newborn born in Tuscany was evaluated for the first time at the Pediatric Immunology Unit, Meyer Children's Hospital, Florence, Italy, a week after birth, following an abnormal result in her neonatal screening card identified at the Immunology Laboratory, responsible for daily neonatal screening for immunodeficiencies across Tuscany.

The patient's neonatal screening showed absent T-cell re-

ceptor excision circles (TREC) and low κ -deleting recombination excision circles (KREC) expression.

The patient's family history revealed no significant immune disorders, autoimmune diseases, consanguinity or unexplained early sudden deaths. She had a healthy 3-year-old brother.

The patient was born full-term (38+3 weeks) but small for gestational age. The perinatal course was uneventful. She had neonatal jaundice that did not require phototherapy. Since birth, she had remained healthy except for a mild episode of rhinitis. A physical examination revealed no abnormalities or dysmorphic features. After the clinical immunological evaluation, blood tests were performed; details are shown in Table 1.

According to the last definition of SCID¹, leaky SCID was

Table 1. Blood tests performed at the initial evaluation, after 2 months and at last follow-up (16 months after hematopoietic stem cell transplantation) with age-adjusted reference ranges.

Blood tests	First evaluation	Evaluation after 2 months	Normal values at 0-3 months	Last follow-up at 16 months after HSCT	Normal values at 1-2 years
WBC, cells/ μ L	1,740	1,370	5,000-15,000	18,060	3,500-14,000
Lymphocytes, %	28.4	26.5	40-80	17.3	30-70
Monocytes, %	28	30.7	2-15	5.7	2-15
Eosinophils, %	11.1	8.7	0-6	12.7	0-6
C-reactive protein	Negative	Negative	-	Negative	-
IgG, mg/dL	525	689	150-630	1,060	320-990
IgA, mg/dL	<5	<5	5-10	75	20-80
IgM, mg/dL	90	151	10-70	314	50-180
B cells, % (cells/ μ L)	11 (46)	9 (26)	(300-2,000)	34.58 (1,079)	(720-2,600)
CD3 ⁺ T cells, % (cells/ μ L)	22 (89)	33 (92)	(2,500-5,500)	33.6 (1,048)	(2,100-6,200)
CD4 ⁺ T cells, % (cells/ μ L)	16 (64)	25 (70)	(1,600-4,000)	22.5 (703)	(1,300-3,400)
CD8 ⁺ T cells, % (cells/ μ L)	4 (18)	6 (16)	(560-1,700)	9.5 (297)	(620-2,000)
NK cells, % (cells/ μ L)	63 (256)	54 (150)	(170-1,100)	27.5 (861)	(180-920)
CD4 ⁺ naive T cells, %	24	25	-	NA	-
TREC expression	Absent	Absent	-	NA	-
KREC expression	Low	Low	-	NA	-
IL-2-induced lymphocyte proliferation, %	-	-	-	90	-
Genetic analysis	-	2 heterozygous mutations in <i>ATM</i> gene (NM_000051.3): c.640delT, p.Ser214Profs*16 (score 11#) and c.5319+2T>C (score 10#)		-	-
Chimerism status	-	-	-	Mixed (86% donor)	-

#Pathogenetic in AlamutTM Visual Plus. HSCT: hematopoietic stem cell transplantation; WBC: white blood cells; TREC: T-cell receptor excision circles; KREC: κ -deleting recombination excision circles; NA: not available; IL: interleukin; Ig: immunoglobulin.

CASE REPORT

diagnosed (50 cells/ μL < T cells <100 cells/ μL , absent TREC expression), and the patient was admitted to the pediatric ward to complete all the necessary further evaluations. Blood tests performed during the follow-up are shown in Table 1.

Among the various tests performed, HLA typing of the patient and her family excluded maternal lymphocyte engraftment and identified the patient's older brother as HLA-identical. Due to the high risk of infection, she received subcutaneous immunoglobulin (Ig) therapy, and prophylactic antibiotic, antiviral, and antifungal treatments were started.

The comparative genomic hybridization (CGH) array analysis resulted normal. Clinical whole-exome sequencing (WES) based on the latest International Union of Immunological Societies (IUIS) classification² was performed and two heterozygous mutations in the *ATM* gene (NM_000051.3), consistent with a diagnosis of ataxia-telangiectasia (AT), were identified (Table 1).

AT is a rare, autosomal recessive neurodegenerative disorder caused by mutations in the *ATM* gene, which plays a critical role in DNA repair and cell cycle control. The disease is characterized by progressive neurological impairment, such as progressive loss of motor coordination (ataxia), dilation of small blood vessels in the skin and mucous membranes (telangiectasia), radiosensitivity, increased cancer risk, and immune system dysfunction leading to recurrent and severe infections.³ Immunodeficiency is variable and mainly involves reduced Ig levels and decreased B and T lymphocytes.⁴ The multisystem nature of AT needs a multidisciplinary approach,

focused on symptomatic and supportive care, including physical and speech therapy, infection control, and surveillance for malignancies, but unfortunately, no curative therapy for this condition has been recognized yet.⁵

In our patient, the initial assumption of leaky SCID was reconsidered in light of the genetic findings, and treatment plans were adjusted accordingly.

The literature review revealed some reports describing patients affected by AT with a hyper-IgM phenotype characterized by combined immunodeficiency, low T- and B-cell counts, hyper IgM, and absent/low IgA and/or IgG.^{6,7} These patients face higher risks of early mortality due to hematological tumors and infectious diseases. Their survival was notably reduced compared to classic AT cases.⁶ Reports also suggested that hematopoietic stem cell transplantation (HSCT) could potentially restore immune-competence and prevent malignancy, though it is not recognized as a standard therapeutic option.^{8,9}

Given the patient's persistent severe lymphopenia and elevated IgM, her case was discussed with multiple transplant centers. Considering the pros and cons, it was decided to proceed with HSCT using her HLA-identical brother as a donor (Figure 1).

Today (+16 months) the patient is doing well and continues to grow. Ig replacement ceased 6 months post-HSCT. No severe or recurrent infections were recorded (either acute or chronic) nor were there toxicities related to the conditioning regimen. She started a psychomotor rehabilitation program with good results: at last magnetic resonance imaging

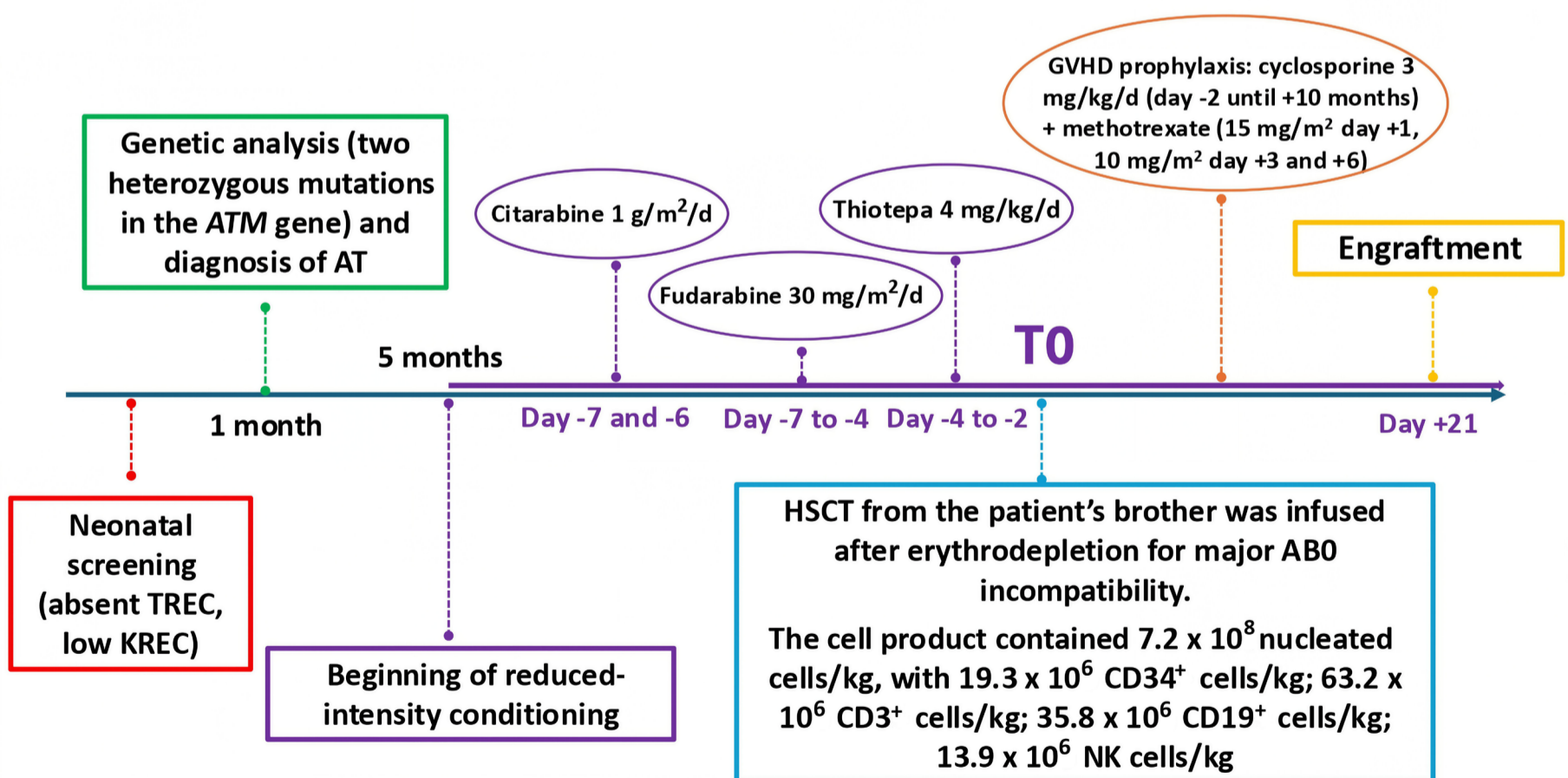


Figure 1. Timeline of major clinical events from abnormal newborn screening to post-transplant engraftment. AT: ataxia-telangiectasia; HSCT: hematopoietic stem cell transplantation; T0: time point at HSCT; GVHD: graft-versus-host disease; TREC: T-cell receptor excision circle; KREC: κ -deleting element recombination circle; NK: natural killer cell.

evaluation of the central nervous system the myelination phenomena were in further progression. Blood tests and chimerism status at the last follow-up are shown in Table 1. We presented the case of a newborn who was recalled following positive neonatal screening due to absent TREC, initially suspected of having leaky SCID. However, subsequent genetic analysis revealed a genetic form of AT.

A review of the literature on AT, coupled with early identification of an immune defect and specific genetic mutations in our patient, led us to explore the potential role of HSCT as an alternative therapeutic approach. Some case reports of patients with AT indicated that HSCT is becoming a promising option, as proper engraftment of healthy cells can potentially restore certain aspects of immunological capacity, prevent malignancies and, as hypothesized in some reports, might even slow down neurodegeneration.⁸⁻¹⁰ However, due to the high risk of mortality resulting from hypersensitivity to ionizing radiation and radiomimetic drugs, a specific conditioning regimen is required. Therefore, although HSCT could be considered a promising therapy for treating immunological defects and preventing cancer in selected patients with AT, this therapy is not widely recognized, and the eligibility of AT patients for HSCT remains an open question requiring further investigation and evaluation.^{8,11}

However, we also analyzed studies describing a more severe AT phenotype characterized by elevated IgM levels (HIGM-AT), requiring different management.¹²

Patients with HIGM-AT, accounting for approximately 10% of cases, typically show a combined immunodeficiency with low T- and B-cell levels, hyper IgM, and low or absent IgA and/or IgG¹³ just like our patient. These patients exhibit the most severe clinical phenotype and face the highest risk of early morbidity and mortality due to the development of hematologic malignancies and infectious diseases. As a result, their survival is significantly reduced compared to patients with classic AT.⁶

Particularly for these patients with HIGM-AT, HSCT was reported as a potential, though debated, treatment option. Weitering *et al.*¹⁴ describe the case of a newborn diagnosed with AT through neonatal screening for SCID, similar to our patient. This case report highlights the clinical and ethical considerations associated with an early diagnosis of HIGM-AT, especially regarding the decision to proceed with allogeneic HSCT. After evaluating all pros and cons, the medical team initially decided to proceed with the transplant. However, it was ultimately not carried out because, at 6 months, the infant's lymphopenia had improved and IgM levels had normalized, thereby losing the HIGM phenotype.

On the contrary, our patient continued to display severe persistent lymphopenia and elevated IgM levels during the follow-up.

Thus, her case was re-evaluated with colleagues from various transplant centers, and given her severe lymphopenia and persistent increase of IgM, as well as the increased risk of infections and the complexity of transplant management and

its complications in case of delay, the decision was made to proceed with an HLA-identical sibling stem cell transplant. The parents were informed that HSCT was chosen to address the immune deficiency and could potentially improve her quality of life, despite not addressing neurological and other complications of her genetic defect.

Recently, a review was published that specifically addresses this topic, outlining the immunological challenges in AT identified through TREC-based newborn screening, the characterization of the HIGM-AT phenotype, and current evidence on preemptive and symptomatic treatments - including the potential role of HSCT - while calling for international collaboration and prospective studies on newborn screening-identified patients.¹⁵

Our case confronted us with the emotional and ethical aspects of patient disease communication, particularly when revising a life-altering diagnosis. Therefore, neonatal screening for immunodeficiencies is a vital step in ensuring early diagnosis and timely intervention, but when discussing preliminary screening results with parents, clinicians must be cautious in their communication approach. Until a definitive diagnosis is established, it is crucial to maintain an open-ended dialogue about potential conditions and in particular their treatment options because, as mentioned before, the screening process identifies a broad range of conditions, some of which may not have curative treatments. Early genetic diagnosis is fundamental in guiding appropriate clinical management, prognosis, and potential therapeutic options, as in this case. Although follow-up is still relatively short, limiting the availability of long-term outcome evidence and representing early feasibility data, our case underscores the value of newborn screening for the early identification of AT patients with severe immunodeficiency, in whom a careful evaluation of the benefits and risks of a potential HSCT is essential.

AT remains a challenging diagnosis due to its multisystem involvement and lack of curative treatment. Indeed, despite the absence of definitive evidence supporting HSCT as a standard therapy for AT, early diagnosis provided an opportunity to explore novel treatment avenues. The continuous expansion of neonatal screening programs and the integration of genetic and precision medicine hold promise for improving outcomes in inborn errors of immunity. Given the rarity of the disease, multicenter collaboration and data sharing are essential to develop evidence-based guidelines and standardized management strategies.

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Contributions

Data curation, formal analysis, investigation, visualization, project administration, writing of the original draft, and writing/review and editing by SR and FB. Data curation, validation, and review and editing by EB, FQ, CC and LL. Formal analysis, investigation, and methodology by FQ and CP. Conceptualization, project administration, supervision, validation, writing/review and editing by CA and FL. All authors read and approved the final version of the manuscript.

Data-sharing statement

Original data are available from the corresponding author upon reasonable request.

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