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Weitering, T.J.; Willemsen, M.A.A.P.; Taylor, A.M.R.; Weemaes, C.M.R.; Burg, M. van der; Berghuis, D.

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LETTER TO EDITOR

Early Diagnosis of Ataxia Telangiectasia Through Newborn Screening for SCID: a Case Report Highlighting the Dilemma of Pre-emptive HSCT

T. J. Weitering[1] · M. A. A. P. Willemsen[2] · A. M. R. Taylor[3] · C. M. R. Weemaes[4] · M. van der Burg[1] · Dagmar Berghuis[5]

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Introduction

Ataxia telangiectasia (AT) is a rare autosomal recessive neurodegenerative disease with progressive cerebellar ataxia, telangiectasias, (hematologic) cancer predisposition, increased radiosensitivity, and a variable immunodeficiency [1]. Historically, diagnosis of AT occurred almost exclusively after onset of neurological symptoms, at age > 2 years. However, in recent years, it has been shown that part of the patients with AT are detected neonatally as a coincidental finding in T-cell receptor excision circle (TREC)-based newborn screening for severe combined immunodeficiency (SCID) [2–4]. To date, there is no curable treatment for AT, although (pre-emptive) allogeneic hematopoietic stem cell transplantation (HSCT) can restore immunity, thereby preventing infectious complications and hematological malignancies [5–7]. This might be of particular interest for patients with an early diagnosis (before the onset of neurological symptoms) and a more severe immunodeficiency. Moreover, regardless of HSCT decision-making, early identification of AT provides opportunities for adequate clinical care at the earliest phases of disease, counseling for family planning and early breast cancer screening for female heterozygous carriers.

Patients with the hyper-IgM AT immunological phenotype (HIGM-AT), which concerns approximately 10% of patients, are typically characterized by a combined immunodeficiency with low T- and B-cells, hyper-IgM (normal to high IgM levels), and low to absent serum IgA and/or IgG(2) levels [1]. These patients have the most severe clinical phenotype and are at highest risk of morbidity and early mortality due to the development of hematological cancer and infectious (lung) disease. Thus, the HIGM-AT patients have a strongly reduced survival as compared to patients with classic AT [1]. Especially for these patients with HIGM-AT, HSCT presents a potential, yet debatable treatment option. Here, we describe an infant with AT diagnosed after SCID newborn screening. Although diagnosis of AT by newborn screening has been described before [2–4], our case highlights the clinical and ethical considerations associated with a very early diagnosis of (HIGM-)AT, in particular those considerations associated with the decision on whether to proceed to allogeneic HSCT.

Case Description

The patient was born at term after an uneventful pregnancy, as the first child to non-consanguineous Caucasian parents with an unremarkable family history. The infant was in good clinical condition when referred after positive TREC-based newborn screening for SCID (TREC copies 8/uL blood; cut-off 10). Follow-up immunological tests ruled out classical SCID, but showed a mild T- and B-cell lymphopenia at 2 weeks after birth (Fig. 1A, B) with normal levels of (maternal) IgG and IgM and absent IgA (Fig. 1C). After a

M. van der Burg and Dagmar Berghuis contributed equally to this work.

✉ Dagmar Berghuis
d.berghuis@lumc.nl

1 Willem-Alexander Children's Hospital, Laboratory for Pediatric Immunology, Leiden University Medical Center, Leiden, the Netherlands

2 Department of Neurology – Pediatric Neurology, Radboud University Medical Center, Nijmegen, the Netherlands

3 Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, UK

4 Department of Pediatrics, Radboud University Medical Center, Nijmegen, the Netherlands

5 Willem-Alexander Children's Hospital, Department of Pediatrics, Division of Pediatric Immunology and Stem Cell Transplantation, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, the Netherlands

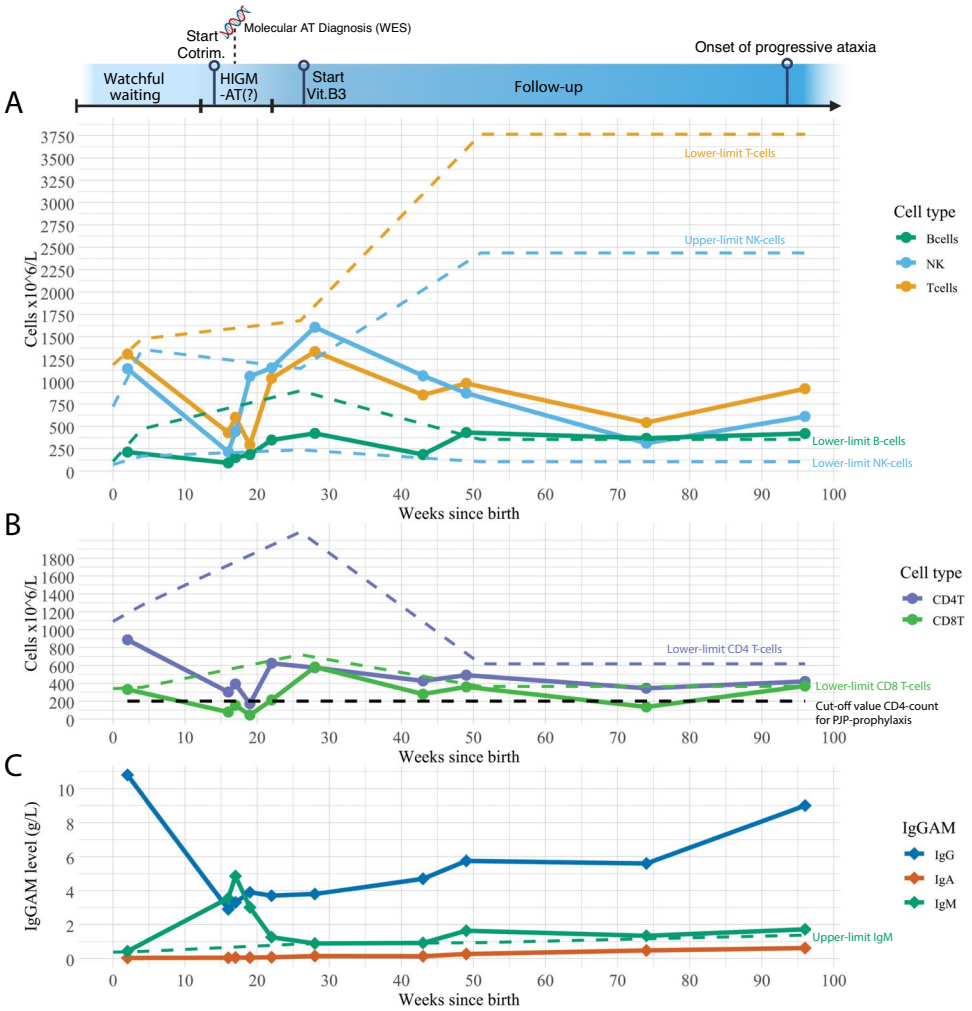

Fig. 1 Overview of flow cytometric immune cell counts and serum immunoglobulin levels. **A** Flow cytometric analysis of total T-cell, NK-cell, and B-cell counts over time (in cells $\times 10^6$/L). The upper and/or lower limits of normal (age-matched) values for (total) T-cells (orange), B-cells (green), and NK-cells (light-blue) are provided, using interrupted lines. **B** CD4 (purple) and CD8 (green) T-cell counts over time. Black interrupted line: cutoff value for *Pneumocystis jirovecii* pneumonia-prophylaxis. The lower limits of normal (age-matched) values for CD4 (purple) and CD8 (green) T-cells are shown by interrupted lines. **C** Total IgG (blue), IgA (orange-red), and IgM (green) serum levels (g/L). Green interrupted line: upper limit of normal (age-matched) value for IgM serum level. The upper and lower limits of normal values for the different immune parameters are based on counts (birth—2 years of age) as reported in the EuroFlow primary immunodeficiency orientation test [12]. The upper limit of normal for IgM serum levels is based on levels reported by Bayram et al. [13]

3-month watchful waiting period, the infant was still in good clinical condition but the laboratory results were unfavorable, with progressive T- and B-cell lymphopenia, decreasing serum IgG, persistent IgA deficiency, and hyper-IgM (Fig. 1; weeks 16–24). Based on a CD4 count $< 200 \times 10^6$/L at age 4 months, *Pneumocystis jirovecii* pneumonia (PJP)-prophylaxis (cotrimoxazole) was started and whole exome sequencing with a primary immunodeficiency filter was performed. This resulted in the identification of two compound heterozygous pathogenic [8–10] mutations in the ataxia telangiectasia mutated (*ATM*) gene (c.5979_5983delTAAG, p.(Ser1993Argfs*23); c.7875_7876delinsGC, p.(Asp2625_Ala2626delinsGluPro)). The patient's cells lacked ATM kinase activity, confirming the diagnosis of classic AT (Supplemental Fig. 1). Based on the results of a recent clinical study, in which vitamin B3 improved ataxia neurological scores as well as IgG levels in patients with AT, we started treatment with nicotinamide riboside (vitamin B3) at age 6 months (250 mg once daily) [11].

The combination of the genetic diagnosis, complete lack of ATM kinase activity, and the immunological parameters suggested a HIGM-AT phenotype in this infant, who was otherwise still in excellent clinical condition. Since HIGM-AT is associated with a significantly increased risk of recurrent (pulmonary) infections and/or hematological malignancies at relatively young age [1], the treating physicians considered pre-emptive allogeneic HSCT for this child. Although literature on allogeneic HSCT for AT is limited, cases of successful (pre-emptive) HSCT have been described, employing reduced intensity conditioning regimens [5–7].

Several medical and ethical considerations about allogeneic HSCT in this child were discussed within an international multidisciplinary group of experts: (1) successful allogeneic HSCT would restore the severe immunodeficiency and be beneficial for prevention of infections and hematological malignancies; (2) a pre-emptive approach would reduce the transplant-related risks associated with pre-existing infections and/or malignancy and a neurodegenerative status of the child; (3) successful allogeneic HSCT might have an impact on neurodegeneration in patients with AT: a few case reports on (pre-emptive) allogeneic HSCT for AT

have suggested a slowdown of neurodegeneration in these patients as compared to non-HSCT treated AT patients [5, 6]. In addition, mouse studies on HSCT in AT have shown improvements in motor and ataxia scores after HSCT [14]; and (4) the nature of AT, a DNA double-stranded-break-repair disorder, increases the risks of (severe) side effects of the conditioning regimen for HSCT and warrant a reduced intensity conditioning regime. Based on these considerations and after careful discussion of the potential risks and benefits of allogeneic HSCT with the parents of the child, it was decided to explore donor options for allogeneic HSCT and re-assess the immunological status of the patient to confirm the HIGM-AT phenotype.

Additional in depth T- and B-cell flow cytometry including TCR repertoire analysis (using a flowcytometric kit of 24 Vbeta's) demonstrated very low naïve T- and B-cell counts, with normal memory T cell subsets but reduced class-switched memory B cells. TCR repertoire analysis demonstrated normal diversity with relatively normal Vbeta usage (Supplemental Fig. 2). These characteristics are all known immunological hallmarks of AT [15] and were compatible with the HIGM-AT phenotype. HLA-typing and a subsequent donor search revealed availability of a 10/10 matched unrelated donor. However, at age 5–6 months, a spontaneous improvement of the immunological parameters occurred (Fig. 1): T- and B-cell counts increased to near-normal levels, and IgG and IgM levels were in the normal range for age. The patient could no longer be considered to suffer from a HIGM-AT phenotype. In dialogue with both the expert team and the parents, the preparations for allogeneic HSCT were put on hold; PJP-prophylaxis was discontinued, and a watchful waiting approach was resumed. Currently, at age 22 months, the child is in shared follow-up at both the Dutch expertise center for AT (RadboudUMC, Nijmegen) and the pediatric immunology and stem cell transplantation department of the Leiden University Medical Center and is still being treated with vitamin B3. She is in good clinical condition with acceptable T- and B-cell counts and Ig levels. She has recently recovered from an uncomplicated primary *Varicella* infection (chickenpox). Physical examination shows mild cerebellar ataxia and dystonic posturing of her arms. Monitoring of both her clinical and immunological status will be continued.

Discussion

AT can be one of the incidental findings of newborn screening for SCID, although not all patients with AT have reduced TREC levels at birth. In all AT cases, identified via newborn screening or retrospectively analyzed, TREC levels were below established cutoff values albeit not in the "urgent positive" range as commonly observed in SCID cases (complete absence of TREC) [2–4, 16]. Low TREC levels in infants with AT could indicate more severe lymphopenia, possibly increasing the risk of recurrent infections and/or malignancies and strengthening the indication for (pre-emptive) allogeneic HSCT. A positive association between IgA deficiency, IgG2 deficiency, lymphopenia, and overall survival has been demonstrated in patients with AT [1, 17]. Additionally, a recent longitudinal follow-up report of immune parameters in AT patients demonstrates progressive depletion of lymphocytes and immunoglobulins over time [18]. Such a decline of immune parameters over time has also been reported in a small cohort ($n=4$) of patients with AT diagnosed by newborn screening [3]. However, the follow-up of these newborn screening-diagnosed patients has been relatively short, and considerations with regard to the option of (pre-emptive) HSCT for these specific cases have not been described. We believe that HIGM-AT patients with a SCID phenotype may benefit from pre-emptive HSCT, since particularly these patients are at increased risk of morbidity and early mortality due to development of hematologic cancer and infectious (lung) disease [1]. It is this subgroup in which we think the transplantation-associated risks [19] are in balance with the potential benefits, i.e., correcting the immunodeficiency and reducing the risk of (hematological) cancer and recurrent and/or severe infections [5–7]. Moreover, a potential positive impact on the course of neurological deterioration might further contribute to this decision for HSCT [5, 6, 14]. The case presented here, initially considered to be HIGM-AT, demonstrated improvement of T cell counts and immunoglobulin levels during follow-up. This specific course highlights the potential medical and ethical vulnerabilities regarding both an early diagnosis of the HIGM-AT phenotype and the decision for pre-emptive HSCT in this patient group. Although HSCT has been performed in young patients with AT [5–7], no reports are available on HSCT for newborn screening-diagnosed AT. In addition, the significance of early start of vitamin B3 treatment on the disease course in our case remains uncertain.

Overall, in our opinion, detailed information on the natural course of immune parameters in newborn screening-diagnosed patients with AT is lacking, which hampers identification of early predictors of a more benign or adverse clinical outcome and, subsequently, an indisputable indication for pre-emptive HSCT in this specific early-diagnosed subgroup of AT patients. Therefore, our case illustrates the need for an international collaboration between experts in AT and HSCT, to further chart the natural course of both immune parameters and clinical status of these patients, including the outcomes of patients that may undergo HSCT.

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Author Contribution DB diagnosed the patient, interpreted clinical data, organized discussions with the international multidisciplinary group of experts as well as follow-up of the patient; MAAPW was involved in discussions with the international multidisciplinary group of experts and participated in follow-up of the patient; AMRT, TJW, and MvdB were involved in generation and interpretation of in-depth molecular and/or immunological analyses; TJW wrote the initial draft of the manuscript and created tables and figures; and CMRW provided additional clinical follow-up data; all authors revised and approved the final manuscript.

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Data Availability All data generated or analyzed during this study are included in this published article and its supplementary information.

Code Availability Not applicable.

Declarations

Ethics Approval This is a case report with retrospective data. The parents of the patient provided informed consent for registration and future use of clinical data in the "LUMC Biobank Kindergeneeskunde/afweerstoornissen," which was approved by the board of directors (March 20, 2017, reference number: B17.001/Sh/sh).

Consent for Publication Freely given, written consent was obtained from the parents of the patient.

Conflict of Interest The authors declare no competing interests.

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