

CASE REPORT

The significance of medical history and its impact on the early diagnosis of inborn errors of immunity

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ABSTRACT

Inborn errors of immunity (IEI) are genetically determined disorders which present clinically as increased susceptibility to infectious, autoinflammatory, or autoimmune diseases, potentially leading to fatal outcomes. Some doctors omit collecting family history, an element of the examination that allows for initial risk stratification of the disease and permits further detailed diagnostics. Currently, unfortunately, the role of medical history is downplayed by primary care physicians in favour of diagnostic tests. The availability of genetic tests in most countries is low, so we would like to use examples to emphasise the enormity of the role of anamnesis, the simplest part of the patient's examination.

The medical history provided valuable information that raised suspicions of IEI. Consequently, genetic studies were conducted for meticulous diagnoses, and then the most effective treatments were administered, including pre-emptive haematopoietic stem cell transplantation.

KEY WORDS:

inborn errors of immunity (IEI), pre-emptive haematopoietic stem cell transplantation (HCT), prospective high-throughput genomics studies, genetic tests, targeted therapy.

INTRODUCTION

Inborn errors of immunity (IEI) are diseases caused by genetic mutations that affect the immune system's ability to fight pathogens, cope with the microbiota, or regulate autoimmunity and inflammation. More than 500 IEIs have been described, and many are life-threatening and require curative therapy.

Patients suffering from IEIs present with multiple severe infections, autoimmune diseases, non-neoplastic lymphoproliferation, and early neoplastic transformations. If left untreated, IEI can lead to rapid death. Therefore, early diagnosis plays a huge role [1, 2]. Immediate treatment is also necessary. This is particularly important

for people with severe combined immunodeficiencies (SCID) and for fatal diseases following exposure to a specific pathogen, such as influenza.

In countries where newborn screening is used, the early detection of serious, life-threatening IEIs has also been addressed. Early diagnosis of severe combined and combined immunodeficiencies and agammaglobulinaemia is possible [3, 4]. There is currently no study on newborn screening for IEIs in Poland. Between 2018 and 2021 a transborder Polish-German study co-financed by the European Union was performed in one region in Poland and 2 German regions. Conducting the screening is substantively justified, and we hope to launch such programs in the coming years [5, 6]. Therefore, the knowl-

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edge of gynaecologists, neonatologists, and paediatricians about the importance of family history and early clinical symptoms of IEL is important. Early diagnosis of SCID gives a chance to implement treatment, such as haematopoietic cell transplantation (HCT) or gene therapy, at the optimal moment – preferably within the first 3 months of the child's life [3, 4]. In diseases such as X-linked lymphoproliferative disorder syndrome (XLP), diagnosis before Epstein-Barr virus (EBV) provides an opportunity to consider HCT [7, 8]. Therefore, a thorough family history for early diagnosis of rare diseases may impact the child's survival. There are still cases of children who are diagnosed too late and, despite treatment options, lose their chance of survival.

The aim of the publication is to pay attention to the importance of detailed medical history, to present the first symptoms of IEL, as well as the role of early diagnosis and treatment on the basis of our centre's own experience. A positive family history should result in a fast track to specialised treatment. Family history is mandatory not only for immunologists, but also for paediatricians, neonatologists, and gynaecologists. These elements of the examination enable initial risk stratification of the disease and allow for further detailed diagnostics [3].

1. In the event of a miscarriage, the week of pregnancy and the cause of the miscarriage, the sex of the foetus, and the type of genetic or immunological disorder are taken into account.
2. Occurrence of deaths at a young age in the family of unknown cause.
3. Severe recurrent diseases in children, e.g. recurrent opportunistic infections.
4. Severe diseases of the haematopoietic system in young children.
5. Side effects after administration of the BCG vaccine, e.g. development of BCGitis.
6. Presence of known gene mutations in the family.
7. Patient data including the prenatal and perinatal period.
8. Patient's phenotype.

Family history data often suggest the possibility of IEL.

To confirm the clinical diagnosis, a genetic test was performed. High-throughput genotyping allows for the assessment of many genes, which then allows for effective diagnosis in the case of a single-gene disease, and then the implementation of appropriate therapy, often associated with bone marrow stem cell transplantation [7]. International studies show that IEL patients have been transplanted for over 50 years. Thanks to many years of experience, we have identified diseases in which there are clear indications for treatment with HCT (e.g. SCID) and those in which HCT is not applicable (e.g. X-linked agammaglobulinaemia – XLA). However, there is a large group of IEL diseases for which HCT is a treatment dependent on many other concomitant factors. One such disease is XLP.

CASE REPORTS

CASE 1

K.S. is a 13-month-old boy from pregnancy and second delivery, born at 41 Hbd, in good condition, umbilical cord healed properly, vaccinated against hepatitis B and BCG on the third day of life.

In the family history, 4 brothers of the boy's mother died before the age of 7 years, 2 of them due to cancer and 2 others due to multi-organ failure from infections of unclear aetiology. Moreover, the patient's maternal cousin died at the age of 9 years due to infectious mononucleosis. The sister of the child's mother suffers from myasthenia gravis.

A significant family history aroused concern among the child's parents. Unfortunately, many specialists, such as neonatologists and paediatricians, did not see the need for immunological diagnostics. The boy began to suffer from infections of the lower respiratory tract.

During hospitalisation related to the infection, immunological tests were carried out. Hypogammaglobulinaemia was diagnosed.

Next, a genetic test using next-generation sequencing (NGS) was performed, which showed that the boy had a mutation in the SH2D1A gene. The diagnosis was X-linked lymphoproliferative syndrome type 1 (XLP1, OMIM # 308240). Genetic tests confirmed that both the boy's mother and grandmother are carriers of the mutation.

At 27 months of age, the boy underwent preventive allogeneic HCT (allo-HCT). The patient developed cutaneous stage 2 graft-versus-host disease (GVHD). After immunosuppressive treatment was implemented, the symptoms of GVHD disappeared. The patient is in recovery and under observation.

CASE 2

B.M. is a 4-month-old boy from pregnancy 11 complicated by anaemia, polyhydramnios, diabetes, and gestosis in the child's mother, delivery 9 at 35 Hbd, with a birth weight of 3210 g, assessed with 10 Apgar points. The boy was vaccinated against tuberculosis and hepatitis B on the first day of life. No abnormalities, including lymphopaenia, were observed in the blood count.

In the family history – 3 brothers died from SCID. Only the third brother was treated with allo-HCT, but he died of complications after transplantation. In the family history, the mother's brother died in early childhood due to pneumonia. The children's mother was not ill, and the mother's 3 different partners, who were the children's fathers, were also not ill.

Based on the medical interview only, without any specific clinical symptoms, IEL was suspected and the patient was referred to our centre. As a result of genetic tests carried out, SCID T-B+ NK+, linked to the X chromo-

some, was diagnosed. A search for an unrelated donor was planned for bone marrow stem cell transplantation. However, due to severe lower respiratory tract infections, pneumonia caused by both *Pneumocystis jirovecii* and RSV, and then respiratory failure, the boy died.

CASE 3

C.I. is a male patient who was admitted to our clinic at 4 months of age for an HCT procedure.

This child was born from a fifth pregnancy, which was complicated by a SARS-CoV-2 infection in the first trimester and required antibiotic therapy a week before delivery due to an upper respiratory tract infection. This was the fourth delivery, with one previous miscarriage occurring in the medical history at 10 weeks of gestation, and the current delivery occurred at 39 weeks of gestation.

In the family history, one brother died due to SCID, so the boy was under immunological care from birth. During diagnostics, a genetic test was performed, revealing the presence of the pathogenic variant c676C > T(p.Arg226Cys) in the IL2RG gene, detected via the Sanger sequencing method. This variant was found in the hemizygous system, present in both the patient's mother and the patient's deceased brother.

The patient was diagnosed with SCID (SCID T-B+NK-).

Due to the diagnosis of SCID, the boy was qualified for pre-emptive allo-HCT and referred to our centre. Prior to the transplantation, the patient experienced one urinary tract infection; otherwise, he had no infections and had not been vaccinated against tuberculosis. He was on immunoglobulin replacement therapy. Cryopreserved haematopoietic cells from peripheral blood were transplanted from an unrelated donor at 4 months of age.

This patient serves as a positive example of early ICI diagnosis and pre-emptive HCT execution. The diagnosis of the older brother's disease, along with proper management, facilitated an early pre-emptive transplant, thereby increasing the chance of saving the child's life.

This case illustrates the importance of accurately interpreting the medical family history.

DISCUSSION

The aim of our publications is to show the positives and negatives of appropriate interpretation of the interview. In countries such as Poland, where we do not have a screening test, we are left with the correct interpretation of the medical family history. We would like to emphasise that even a spectacular interview in 2 of the 3 presented cases (first and second) did not convince neonatologists and paediatricians to make early immunological consultation. However, compared to recent years, the awareness of the presence of ICI is increased. Unfortunately, there are still cases in which the diagnosis of ICI is made too

late and the child dies of perinatal complications, e.g. opportunistic infections. Errors in early diagnosis made by neonatologists and paediatricians will still occur commonly if the medical family history is not completed and well interpreted, as it was in the case of the second patient. In this case, the doctors believed the mother's opinion that changing the partner would solve the problem. They did not realise that the entire interview strongly indicated X-linked inheritance, so the change of partner had no effect on the risk of this woman's next son. In the application – with such an interview and the lack of medical documentation, the neonatologist should contact the immunologist. Unconfirmed medical information from a parent should be treated with caution. This indicates that the crucial value of medical family history in the early diagnosis of rare diseases has, for some doctors, only theoretical meaning. Therefore, there are still problems with converting this theory into everyday life practice. However, we are helpless in the face of the first diseases in the family. For this reason, it is important to know that lymphopaenia may be indicative of SCID, or to consider SCID early based on the spectrum of clinical symptoms. A diagnosis before 3 months of age is rare, so the prognosis for children is worse. In XLP diseases, diagnosis is usually possible after exposure to EBV infection – haemophagocytic lymphohistiocytosis or lymphoma develops [7, 8]. It may still be valid to say that at least one child in a family must die for a sibling to be diagnosed with the disease. In the case of the second patient, the diagnostic process was implemented too late and the patient died because of opportunistic infection. Immediately after birth, a cytometry test should be performed, which would indicate whether the baby is suffering from SCID [9].

We need to remember that late diagnosis may result in a lost chance of recovery or even the child's death. That is why it is crucial that the whole family and newborn child stay under the care of immunologist/genetics if are premises of ICI. For unknown family gene mutations, the best diagnostic method is NGS. When the mutation is known, the best test is the Sanger sequencing method. Due to international research, in families with known gene mutations, the laboratory test such as the subpopulation of lymphocytes on the first day of life could raise the first suspicions of ICI [2]. Testing of the subpopulation of lymphocytes on the first day of life allows a diagnosis in SCID to be made. In other diseases, like XLP, more advanced diagnostic procedures are needed, including NGS. However, then the first serious infection should indicate the need for a genetic/immunological consultation. In a severe phenotype, diagnosis at birth would give a chance to save the child's life through early pre-emptive HCT [8, 10]. In 2 out of 3 patients, the pre-emptive HCT procedure was selected. Unfortunately, one out of those 3 patients died before HCT. The above examples of our patients show that if the family is under constant immunological care, the risk of unverified diagnosis in siblings is minimal. We analysed

and consulted internationally a case with XLP, and finally we chose to select HCT as the best possible option for our patient. However, according to the literature, the alternative treatments to HCT should be considered if available, and they should allow a good quality of life.

CONCLUSIONS

A well-collected and correctly interpreted medical history is crucial for the early diagnosis of rare diseases, including IEI. This significance becomes even more pronounced when there is no screening test available for a particular health condition. Therefore, the cooperation between neonatologists, paediatricians, and immunologists plays a significant role in recognising “red flags” during the collection of a patient’s medical family history. Early diagnosis of IEI in patients with a positive family history provides an opportunity to take action, minimising the risk of perinatal infectious complications and enabling early treatment. Moreover, a quick genetic diagnosis is possible if the gene mutation carried by the parents is known. The time needed to prepare a child for pre-emptive HCT is about 1–2 months, making prenatal testing unnecessary.

DISCLOSURES

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REFERENCES

1. Abraham RS. How to evaluate for immunodeficiency in patients with autoimmune cytopenias: laboratory evaluation for the diagnosis of inborn errors of immunity associated with immune dysregulation. *Hematology Am Soc Hematol Educ Program* 2020; 2020: 661-672.
2. Cooper MA, Zimmerman O, Nataraj R, et al. Lifelong immune modulation versus hematopoietic cell therapy for inborn errors of immunity. *J Allergy Clin Immunol Pract* 2021; 9: 628-639.
3. Dąbrowska A, Grzešk E, Urbańczyk A, et al. Extended list of warning signs in qualification to diagnosis and treatment of inborn errors of immunity in children and young adults. *J Clin Med* 2023; 12: 3401.
4. Demir DD, Asnaashari K, Rezaei N, et al. Management of inborn errors of immunity in the genomic era. *Turk Arch Pediatr* 2022; 57: 132-145.
5. Nakano Y, Rabinowicz R, Malkin D. Genetic predisposition to cancers in children and adolescents. *Curr Opin Pediatr* 2023; 35: 55-62.
6. Giżewska M, Durda K, Winter T, et al. Newborn screening for SCID and other severe primary immunodeficiency in the Polish–German transborder area: experience from the first 14 months of collaboration. *Front Immunol* 2020; 11: 1948.
7. Grzešk E, Kołtan S, Dąbrowska A, et al. Case report: cellular therapy for hydroa vacciniforme-like lymphoproliferative disorder in pediatric common variable immunodeficiency with chronic active Epstein-Barr virus infection. *Front Immunol* 2022; 13: 915986.
8. Lankester AC, Neven B, Mahlaoui N, et al. Hematopoietic cell transplantation in severe combined immunodeficiency: the SCETIDE 2006–2014 European cohort. *J Allergy Clin Immunol* 2022; 149: 1744-1754.e8.
9. Reilly L, Emonts M. Recurrent or unusual infections in children – when to worry about inborn errors of immunity. *Ther Adv Infect Dis* 2023; 10: 20499361231162978.
10. Slatter M, Lum SH. Personalized hematopoietic stem cell transplantation for inborn errors of immunity. *Front Immunol* 2023; 14: 1162605.