Prevention is Better than Cure! Can We prevent Primary Immune Deficiency Diseases?

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Abstract

Severe immune deficiencies are often fatal in young childhood unless recognized and treated with a hematopoietic stem cell transplant (HSCT) timely. The majority of the immune deficiencies are monogenic diseases and may affect multiple children in the affected family. While diagnoses and treatment of the affected child are of immediate priority, preventing these diseases in subsequent pregnancies is paramount. In this paper, we discuss the importance and ways of antenatal detection of inborn errors of immunity (IEI) and present a few case scenarios highlighting the need to consider different modalities for the diagnosis of these diseases in the fetus.

Keywords: Amniocentesis, Antenatal testing, Chorionic villous, Cordocentesis, Inborn Errors of immunity, Sampling.

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Introduction

Primary immune deficiency diseases, better known as IEI, are a group of genetically and clinically heterogeneous diseases that predispose affected individuals to infections, autoimmunity, allergy, and malignancies. Although a diverse group of disorders, IEIs can be broadly classified into B cell defects, T cell defects, phagocytic disorders, and complement deficiencies. While certain primary immune deficiencies are mild, many of them are severe and affect the quality and quantum of life significantly.

Immunological tests can pick up the diagnosis in some of these conditions; for example, low immunoglobulins (Igs) and absent B-cells in a boy may point at the diagnosis of X-linked agammaglobulinemia; abnormal dihydrorhodamine test in the appropriate clinical setting is diagnostic of chronic granulomatous disease. It must be noted that immunological tests are screening tools, while genetic tests are confirmatory. Moreover, identifying the underlying genetic disorder is essential to offer antenatal tests in the subsequent pregnancy.[1] Children with severe combined immune deficiency (SCID) often present in a sick state, and transplanting (HSCT) these children may not always be feasible due to their clinical condition and social circumstances. However, one must make every effort to get a genetic diagnosis, as this would help prevent the disease in the next pregnancy. Exome sequencing by next-generation sequencing is now readily available in all major cities and has been a game-changer for the diagnoses of genetic diseases.

Diagnosis of Immune Deficiency in the Fetus

Families with immune deficiency diseases must be offered genetic counseling and antenatal testing in subsequent pregnancies. In the case of a monogenic defect, one can perform Sanger sequencing on the fetal tissue and identify the genetic defect even before birth! Modalities like chorionic villous sampling (CVS), amniocentesis and cordocentesis can provide fetal cells/tissue, which can be subjected to genetic testing. If the fetus is affected, the family can make an informed decision about the discontinuation of the pregnancy in case the disease has a grave prognosis.

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Modalities of Sampling

Antenatal testing provides an opportunity to screen the fetus for genetic disorders. Different sampling techniques are used depending upon weeks of gestation and have been summarized in Table 1.

Clinical and Ethical Dilemma

Antenatal diagnosis raises complex ethical issues for the families in terms of decision-making and for the clinician involved in invasive antenatal testing. The purpose of antenatal testing is timely diagnosis and early termination, hence, preventing the family from being subjected to the mental trauma of an unfavorable clinical outcome. Such a form of invasive testing can be offered only if the previous child has a confirmatory genetic diagnosis. Counseling would be challenging in those diseases with a varied spectrum of clinical presentations. For example, testing a fetus for a possibility of a serious immune deficiency (e.g., SCID) would be justified, as the disease has poor outcomes universally in the absence

Table 1: Invasive sampling methods used for antenatal diagnosis[2]

Technique	*Approach*	*Sample*	*Ideal time*
CVS	Transcervical/abdominal approach to draw samples from the placenta (which are identical to cells from the fetus)	Chorionic villus (placental tissue)	10–13 weeks
Amniocentesis	Transabdominal approach to the amniotic cavity	Amniotic fluid	15–18 weeks
Cordocentesis	Direct puncture of the umbilical vein close to its placental insertion	Fetal blood	≥18 weeks

of HSCT. However, for diseases like hyper IgE syndrome (signal transducer and activator of transcription 3 dominant negative mutation), where the penetration is variable and hence the clinical outcome, the decision on performing antenatal tests would not be straightforward. Genetic counseling must be offered to all families before subjecting them to invasive antenatal tests.

Let us discuss a few clinical cases and understand how we prevent these diseases by performing antenatal tests.

Case Description

Case 1

Master S, a 5-month-old infant, presented with recurrent oral thrush, pneumonia and failure to thrive. Family history was significant for the death of two siblings during early infancy with severe infections. He was diagnosed with SCID but succumbed to severe pneumonia. Parents were counseled, and exome sequencing was performed in the index case, which showed a pathogenic mutation in the Recombination Activating 1 (RAG1) gene posthumously. Both parents were carriers of the same mutation. The family was offered genetic counseling and referred to fetal medicine services.

Antenatal Testing

During the next pregnancy, a CVS was performed at 11 weeks of gestation.

Tissue was processed, and maternal contamination was excluded.

Sanger sequencing for the RAG1 gene was performed.

Fetus had the same genetic mutation as Master S.

As the fetus was affected, the family opted for medical termination of pregnancy.

In the subsequent pregnancy, genetic testing on the CVS sample was normal, and a healthy baby was delivered at term.

Message

- Offering genetic testing is crucial in sick children with immune deficiencies.
- Chorionic villous sampling (CVS), can be performed at 10–13 weeks of gestation.

Case 2

Mrs K had lost a previous child who had multiple infections from a young age. He was diagnosed with chronic granulomatous disease, and genetic testing showed a pathogenic mutation in the Cytochrome B-245 α-Chain (CYBA) gene. Both parents were carriers of the same mutation. She was referred to the fetal medicine services at 14 weeks of gestation with a singleton pregnancy.

Antenatal Testing

Mrs K underwent amniocentesis at 16 weeks of gestation.

Amniotic fluid was sent for Sanger sequencing of the CYBA gene.

Fortunately, the test was reported normal.

Mrs K continued the pregnancy and later delivered a healthy baby.

Message

Amniocentesis is useful for antenatal diagnosis between 15 and 18 weeks of gestation.

Case 3

Mrs C had lost three children with leukocyte adhesion deficiency (LAD) type 1. Integrin β chain-2 (CD18) expression on neutrophils by flow cytometry was absent; however, genetic testing failed to identify a pathogenic mutation. She reported to fetal medicine services at 10 weeks of gestation.

Intervention

As genetic testing was negative in affected children, no genetic test could be performed in the current pregnancy.

At 18 weeks of gestation, cordocentesis was performed, and 10 mL of cord blood was collected.

After excluding maternal contamination, a CD18 assay was performed on cord blood.

Integrin β chain-2 (CD18) expression was noted in 98% of neutrophils, which excluded LAD type 1 in the fetus.

The family opted to continue the pregnancy, and a healthy baby was delivered.

On day 3 of life, CD18 expression on neutrophils was studied and was reported normal.

Message

Cordocentesis can be performed beyond 18 weeks of gestation.

Cordocentesis provides direct access to fetal blood, which can be subjected to flow-based studies to look for protein expression in fetal cells.

Conclusion

Primary immune deficiencies, also known as IEI, are a growing list of genetic diseases.

Offering genetic counseling and antenatal testing in affected families is an extremely important component of the management of these diseases.

Antenatal testing provides an opportunity to diagnose these conditions before birth.

Families can then make informed decisions about the pregnancy.

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