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Inborn errors of immunity in mainland China: the past, present and future

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ABSTRACT

Inborn errors of immunity (IEI), also known as primary immunodeficiency diseases, comprise a group of rare genetic disorders that affect the development or/and function of the immune system. These disorders predispose individuals to recurrent infections, autoimmunity, cancer and immune dysregulations. The field of IEI diagnosis and treatment in mainland China has made significant strides in recent years due to advances in genome sequencing, genetics, immunology and treatment strategies. However, the accessibility and affordability of diagnostic facilities and precision treatments remain variable among different regions. With the increasing government emphasis on rare disease prevention, diagnosis, and treatment, the field of IEI is expected to progress further in mainland China. Herein, we reviewed the development and current state of IEI in mainland China, highlighting the achievements made, as well as opportunities and challenges that lie ahead.

INTRODUCTION

Inborn errors of immunity (IEI), also known as primary immunodeficiency diseases, are a group of genetic disorders resulting from mutations in various genes essential for the development or/and function of the immune system.[1] These disorders predispose affected individuals to recurrent infections, autoimmunity, cancer and other immune dysregulations.[1] IEI, estimated to affect 1% of the global population,[2] with approximately 14 million cases in mainland China, have become a challenging public health issue.

IEI have rapidly developed in mainland China over the past two decades, primarily due to advances in genome sequencing, genetics, immunology and molecular biology. The combination of high-throughput sequencing and functional validation has enabled more patients to receive accurate genetic diagnoses.[3–10] A comprehensive understanding of the molecular mechanisms underlying IEI has laid the groundwork for the clinical application of molecular targeted therapies.[11 12] Moreover, gene therapy is emerging as a promising curative treatment strategy for IEI, in addition to allogeneic haematopoietic stem cell transplantation (HSCT).

Despite these advances in diagnosis and treatment, challenges remain. For example, the lack of a national newborn screening (NBS) programme leads to delayed diagnosis, severe complications and adverse reactions to vaccines in some types of IEIs.[13–15] In addition, although there is a relatively large number of patients with IEI, the discovery of novel disease-causing genes in mainland China lags behind that of developed countries.[1 6] Herein, we reviewed the development and current state of IEI in mainland China, highlighting the achievements made, as well as the opportunities and challenges that lie ahead.

The history and development

In the 1960s, a few cases potentially related to IEI were reported in mainland China.[16] In the early 1980s, Dr Feng, a researcher at Beijing Children's Hospital, successively reported congenital thymic dysplasia and combined immunodeficiency disease.[17 18] These pivotal findings marked the initial recognition of IEI within the medical community of mainland China. In 1998, the Chinese Pediatric Immunology Society established screening and diagnostic procedures, as well as a collaborative network comprising 14 specialist centres for IEI, in addition to an IEI patient registration system.[16 19] From then on, regular meetings and training courses have been organised to enhance the knowledge, skills and practice of clinicians in the field of IEI. Several centres have retrospectively analysed the diagnosis of various types of IEIs, with the majority of patients being diagnosed based on clinical manifestations and immunological tests.[20–24] Among them, antibody deficiency has been reported to be the most common IEI.[20–24]

Over the past two decades, especially with the introduction of next-generation sequencing in clinical diagnostics in mainland China, patients with IEI have gained earlier access to genetic diagnoses and precision therapies. A study summarising results from seven cities in mainland China revealed an estimated IEI prevalence of approximately

2 in 1 million, of which nearly half of patients remain genetically undiagnosed.[3] This may be attributed to the wide variation in the accessibility and affordability of diagnostic facilities among different regions, potentially leading to an underestimation of the actual prevalence. Additionally, an increasing number of single-centre studies have reported a couple of cohorts of monogenic IEI, including X-linked agammaglobulinemia (XLA),[25 26] hyper-IgM syndrome (HIM),[27–29] chronic granulomatous disease (CGD),[30–32] Wiskott-Aldrich syndrome (WAS),[33] severe combined immunodeficiency disease (SCID)[34 35] and adenosine deaminase deficiency.[10] In 2018, mainland China reported for the first time a new IEI-causing gene, *RASGRP1*, which leads to the development of autoimmune lymphoproliferative syndrome-like disease.[6] Subsequently, several rare IEI types with novel mutations in known genes were reported.[7 36] As for treatment, in addition to previous symptomatic strategies, numerous specialist centres have conducted successful transplantations for different types of IEIs, such as SCID, HIM, WAS, CGD and X-linked inhibitor of apoptosis (XIAP) deficiency.[37–41] Currently, dedicated HSCT centres for IEI have been established in Beijing, Shanghai and Chongqing as core locations.

In recent years, the Chinese government has increasingly emphasised the prevention, diagnosis and treatment of rare diseases. To this end, China's First National List of Rare Diseases, which includes XLA, combined immune deficiency, WAS, familial Mediterranean fever, severe congenital neutropenia and X-linked lymphoproliferative syndrome, was published in 2018.[42] This important initiative aims to raise awareness of rare diseases among clinicians and the public, and promote genetic screening for rare disease. Furthermore, the Guidelines for the Diagnosis and Treatment of Rare Diseases, including the afore-mentioned IEIs, were developed in 2019 to standardise the diagnosis and treatment procedures.[43] The first National Congress of IEI was successfully held in 2022, fostering knowledge exchange and collaboration. These efforts are expected to further advance the development of precision diagnoses and treatments for IEI.

Prevention and screening

Patients with IEI often remain undiagnosed during the early stages, resulting in missed opportunities for optimal treatment. Delayed diagnosis or unidentified cases of IEI may lead to recurrent infections, severe complications and even premature death. Furthermore, repeated hospitalisations result in substantial medical expenses and increase the mental and economic burden on patients and their families. Prenatal diagnosis or NBS can identify IEIs in fetuses or newborns, thereby facilitating early diagnosis and intervention, which are crucial strategies for IEI management.

Prenatal diagnosis

In mainland China, some hospitals have established genetic counselling departments to provide families, particularly those with a family history, with genetic counselling for IEI. Currently, available techniques for prenatal diagnosis of IEI include chorionic villus biopsy, amniocentesis, cordocentesis and non-invasive prenatal testing. These methods analyse fetal DNA to identify genetic mutations associated with IEI. Several studies have reported successful cases of prenatal diagnoses using these approaches, such as CGD,[32 44 45] WAS,[46] SCID,[35] XLA[47] and XLP.[48] Nevertheless, certain invasive techniques carry risks of miscarriage. Additionally, clinical decisions-making based on genetic test results can be complex. Therefore, the ethical issue associated with prenatal diagnosis is a concern.

Newborn screening

Early screening of newborns not only improves diagnostic rates and outcomes for IEI but also helps avoid vaccine-related adverse events for several IEI entities.[13–15] The maturation processes of T cells and B cells produce T-cell receptor excision circles (TRECs) and kappa-deleting recombination excision circles, respectively, which can be used for newborn screening of congenital T cell or/and B cell deficiencies.

SCID, characterised by a deficiency in T cells, is often fatal within the first year of life. NBS facilitates the early detection of SCID and the initiation of HSCT, resulting in improved long-term survival rates and enhanced quality of life.[49] NBS for SCID has been implemented in the USA and several European countries.[50–54] Given that approximately one patient with SCID can be found per 33 000 neonates,[50] it is estimated that roughly 450 out of the 15 million newborns annually in mainland China may be afflicted with SCID. Consequently, NBS for SCID can significantly contribute to early diagnosis and timely initiation of HSCT. At present, several hospitals have commenced pilot projects for TREC NBS. It is anticipated that NBS for SCID will be increasingly implemented across a greater number of cities to improve the overall effectiveness of early detection and treatment.

In addition, Beijing Children's Hospital is spearheading a multicentre clinical study based on targeted sequencing, which is aimed at 465 disease-causative genes, covering IEI-related genes such as XLA, WAS, CGD, among others.[55] Preliminary findings suggest that this research could become a first-tier NBS programme, potentially revolutionising the current state of NBS in mainland China.[55]

Diagnosis

The International Union of Immunological Societies has described 485 IEIs.[56] Despite recent advances in immunology and genetic analysis, diagnosis remains a formidable challenge due to the phenotypic and genotypic heterogeneity of IEI. In mainland China, the diagnostic rate of IEI is merely about 5%,[57] potentially attributable to a deficit of expertise among clinicians and a shortage of genetic testing and diagnostic facilities. Table 1 lists

Table 1 Diagnostic test and treatment available for IEI patients in mainland China

Hospital level	Diagnostic test	Treatment
Primary	CBC and differentials	Antimicrobials
Secondary	In addition to the above: Immunoglobulin levels (IgG, IgA, IgM, IgE)	Antimicrobials Intravenous IG
Tertiary (General)	In addition to the above: 1. C3, C4, CH50, AH50 2. Specific antibody response 3. Basic lymphocyte subset analysis (CD3, CD4, CD8, CD19, CD20, CD16, CD56) 4. Cytokine production (eg, IL-6, TNF-α, IL-8) 5. Genetic testing (eg, TES, WES, WGS)	Antimicrobials Intravenous IG HSCT
Tertiary (IEI Specialised)	Besides the above, including but not limited to the following: 1. Comprehensive lymphocyte subset analysis 2. Lymphocyte proliferation 3. TREC qPCR 4. Granulocyte function tests (eg, dihydrorhodamine test, nitroblue tetrazolium test) 5. NK cytotoxicity studies 6. Specific protein levels (eg, WASp, BTK) 7. Pathway function (eg, JAK-STAT, NF-κB)	Antimicrobials IVIG Biologics Targeted therapy HSCT

BTK, Bruton tyrosine kinase; CBC, complete blood count; HSCT, hematopoietic stem cell transplantation; IG, immunoglobulin G; IL, interleukin; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; qPCR, quantitative polymerase chain reaction; TES, targeted exome sequencing; TNF-α, tumor necrosis factor alpha; TREC, T-cell receptor excision circle; WASp, Wiskott–Aldrich Syndrome protein; WES, whole exome sequencing; WGS, whole genome sequencing.

the diagnostic tests for IEI that are generally accessible in hospitals across various tiers in mainland China.

Biological tests

When a patient is suspected of having IEI, an initial clinical evaluation is commonly performed in many tertiary hospitals, followed by an immunological assessment tailored to the suspected IEI subtype. This assessment typically includes evaluating the absolute numbers and percentages of basic lymphocyte subsets, immunoglobulins levels and cytokine detection. In specialist centres, additional tests may also be conducted, such as comprehensive lymphocyte subset analysis, lymphocyte proliferation and granulocyte function tests among others. Collectively, these biological tests are essential for understanding the underlying immunological abnormalities and guiding further genetic testing and appropriate management strategies.

Genome sequencing and functional validation

The advent of next-generation sequencing technologies, including targeted exome sequencing (TES), whole-exome sequencing (WES) and whole-genome sequencing (WGS), has broadened accessibility in commercial laboratories across mainland China. These technologies are extensively used for molecular diagnosis in patients with suspected IEI.[58] TES is the most efficient and cost-effective approach when the clinical phenotype and genetic pattern suggest a potential causative gene for IEI. If TES is inconclusive, WES and WGS can be used for further screening, potentially revealing mutations in unknown IEI-causing genes.

Nonetheless, establishing a clear relationship between the candidate disease-causing genes and the complex IEI phenotypes often remains a challenge. Consequently, thorough functional experiments are required to verify that the identified variants cause changes in the associated pathways and phenotypes. For instance, novel compound heterozygous missense mutations in *IL-10R1* were discovered in a patient with neonatal-onset Crohn's disease.[4] Functional studies indicated that the mutation impaired interleukin (IL)-10-induced IL-10R1 phosphorylation, subsequently impairing STAT3 activation and the suppression of inflammatory responses.[4] In children with *Penicillium marneffei* infection, *STAT1* gain-of-function (GOF) mutations were detected, with functional experiments indicating enhanced phosphorylation of STAT1 and impaired IFN-γ and IL-17 responses.[5] Additionally, in a case involving two siblings, a novel IEI-causing gene, *RASGRP1*, causing autoimmune lymphoproliferative syndrome-like disease was identified.[6] The functional experiments suggested defective T-cell activation and proliferation, along with impaired activation-induced cell death of T cells.[6] In another case, a novel heterozygous missense mutation of *NLRC4* was detected in a patient with mild autoinflammation and recurrent urticaria, with functional studies indicating markedly elevated production of IL-1β and IL-6.[7] Furthermore, a novel *STAT3* GOF mutation was identified in a patient with infancy-onset

interstitial lung disease.[8] The functional tests suggested enhanced phosphorylation and transcriptional activity of STAT3.[8] Additionally, two novel mutations in *NLRP12* were identified in patients with autoinflammatory diseases.[9] Functional experiments suggested elevated levels of IL-1β, IL-6 and tumor necrosis factor alpha, as well as increased transcriptional activity of nuclear factor kappa-light-chain-enhancer of activated B cells.[9] These findings underscore the importance of genetic testing combined with functional validation to establish the associations between disease-causing genes and their corresponding disease phenotypes.

Treatment

The primary treatment options for IEI include replacement therapy and HSCT. In recent years, with a better understanding of gene function and disease pathogenesis, precision therapy, such as small molecule drugs targeting mutant proteins or signalling pathways, has been increasingly applied in clinical practice. Moreover, gene therapy is emerging as a promising new approach to compensate for or correct IEI caused by gene defects and abnormalities. Table 1 lists the IEI treatments generally available in hospitals of various tiers in mainland China.

Immunoglobulin G replacement therapy

The regular administration of immunoglobulin G (IgG) replacement therapy is an essential pharmacological treatment for most patients with primary antibody deficiency (PAD). The primary goal is to prevent severe infections and maintain patients' quality of life.[59] As of 2017, intravenous IG for PAD was included in health insurance coverage in mainland China, with a reimbursement ratio of no less than 70%,[60] thereby reducing the financial burden on families. In 2019, an expert consensus was developed concerning IgG replacement therapy for IEI, with the objective of promoting the standardisation of IgG replacement therapy.[61] Given that IgG replacement therapy constitutes lifelong treatment for patients with IEI, factors such as tolerance, medication compliance and quality of life are essential considerations. Intravenous IG may cause numerous adverse effects, whereas subcutaneous IG (SCIG) is associated with fewer side effects, increased convenience, lower costs and improved quality of life. Therefore, SCIG has become the standard treatment for patients with PAD in Europe and the USA.[62 63] Currently, a phase III clinical trial of SCIG replacement therapy is ongoing in mainland China for IEI patients with PAD.

Haematopoietic stem cell transplantation

HSCT is a cure for numerous IEIs. However, due to the varying mechanisms and phenotypes of IEI, formulating a standard approach to HSCT remains challenging. In fact, as far back as 1991, Professor Lu successfully carried out HSCT on a patient with XLA deficiency.[64] In recent years, an increasing number of tertiary centres have performed HSCT for IEIs such as SCID, HIM, WAS, CGD and XIAP deficiency.[37–41] A retrospective study conducted by the Shanghai Children's Medical Center showed that the 2-year overall survival (OS) rate was 78.7% among 47 patients with IEI who underwent allogeneic HSCT between 2013 and 2018.[37] The Children's Hospital of Chongqing Medical University has also performed over ten different types of IEI for HSCT, with notable outcomes such as a 5-year OS rate of 84% for patients with WAS between 2007 and 2017,[38] an 18-month OS rate of 86.4% for patients with CGD from 2012 to 2018,[39] and a 2-year OS rate of 82.35% in patients with HIM from 2009 to 2019.[40] Importantly, in an intensive care unit, Beijing Children's Hospital successfully performed a conditioning-free HSCT for an SCID patient with life-threatening infection, providing a treatment opportunity for critically ill patients.[65]

Targeted molecular therapies

The advances in understanding of the mechanisms underlying immune deficiencies have facilitated the development of targeted therapies, such as small-molecule drugs or monoclonal antibodies. These therapies have been designed to specifically target proteins or immune signalling pathways involved in the pathogenesis of IEI. Recently, small molecule targeted therapies, as a new approach in IEI treatment, have been increasingly employed in mainland China. Patients with lipopolysaccharide responsive beige-like anchor protein or cytotoxic T-lymphocyte-associated protein 4 deficiency, who presented with chronic diarrhoea, recurrent infections, hypogammaglobulinemia, diminished regulatory T cells and increased circulating follicular helper T (cTfh) cells, showed significant improvements in controlling enteropathy and a noticeable decrease in the frequency of cTfh cells following treatment with abatacept.[11] A patient with sideroblastic anaemia, immunodeficiency, periodic fevers and developmental delay demonstrated a good response to thalidomide in terms of down-regulation of inflammatory responses.[12] A patient with STAT3 GOF disease showed significant improvements in rash, asthma and symptoms of pulmonary hypertension after being treated with ruxolitinib (unpublished data). Sirolimus also demonstrated significant efficacy in alleviating the symptoms of patients with activated PI3K syndrome (unpublished data). Taken together, these pioneering interventions highlight the potential of targeted therapies for improved clinical outcomes in mainland China in the future.

Gene therapy

In recent years, significant advances have been made in the field of gene therapy, making it a potentially curative treatment for IEI. Gene therapy for IEI involves the introduction of a functional copy of the defective gene either via gene addition or gene editing methodologies to ameliorate the disease. Retrovirus-based vectors and CRISPR/Cas9-based gene editing techniques have been successfully employed in human gene therapy to correct

IEI.[66] In mainland China, gene therapy for IEI is on the way of preclinical research stages in certain hospitals and research institutions. The initiation of clinical trials for gene therapy in IEI is eagerly anticipated, and it is expected that there will be commercialised gene therapy products that will benefit patients with IEI.

Future challenges and opportunities

Despite the significant progress made in the diagnosis and treatment of IEI in mainland China over recent decades, several challenges exist. In terms of diagnosis, numerous factors can lead to delayed referral of patients to tertiary hospitals or institutions capable of diagnosing IEI, such as a lack of adept primary care clinicians capable of promptly identifying IEI, and a generally low level of public awareness about IEI, inclusive of patients and their family members. Moreover, even if a IEI are suspected, the availability of diagnostic facilities may be limited in remote areas. Also, in cases where genetic sequencing is accessible, there might be a deficiency in the authoritative interpretation of novel variations in known or unknown genes. Additionally, the lack of NBS results in missed optimal treatment opportunities for some patients. With regard to treatment, a significant number of patients with IEI require multiple episodes of hospitalisation and extended stays prior to a clear diagnosis.[60] Furthermore, the median annual cost of patient hospitalisation account for over 40% of total household consumption expenditure, consequently posing a significant financial burden.[60]

Given that mainland China constitutes approximately 18% of the global population, there would be a substantial number of patients with IEI. This provides a unique opportunity for discovering novel disease-causing genes and developing effective treatments through clinical trials. For the advances in the field of IEI, several measures need to be taken. First, medical education should be promoted among primary care clinicians to enhance their abilities in identifying and referring complicated cases of IEI. Training courses are also necessary for the specialists to ensure accurate diagnosis and treatment of IEIs. In addition, national and international multicentre collaborations will enable the sharing of experiences and contribute to progress in the field. Furthermore, enormous efforts are needed for the application of newborn screening, identification of novel IEI-causative genes, clarification of underlying disease mechanism and development of new drugs and treatment modalities. By implementing these measures, significant improvement can be made in the diagnosis and treatment of IEIs, thereby advancing this field in mainland China.

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