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Primary Immunodeficiency in South China: Clinical Features and a Genetic Subanalysis of 138 Children

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Abstract

Objectives: We analyzed the clinical features of 138 patients with primary immunodeficiency (PID) and performed genetic testing on a subset of patients in order to complete gaps in research on PID in South China and thus improve pediatricians' ability to recognize and diagnose PID.
Methods: We performed a retrospective analysis based on the medical records of PID patients hospitalized in our institution between May 1999 and June 2012. Gene sequencing was performed in 59 cases.
Results: Children with PID usually present with fever and repeated infections that generally affect the respiratory and digestive tracts. Growth retardation is observed in some cases. Of the 138 patients, 113 were boys, median age at onset was 5 months (range, 0-119 months), and age at diagnosis was 10 months (2-159 months). A family history of repeated infection or death of family members in infancy because of recurrent infections was recorded in 20 cases (14.49%). Antibody defects were detected in 48 cases (34.78%), combined immunodeficiency disease in 45 cases (32.61%), and other well-defined immunodeficiency syndromes in 45 cases (32.61%). Of the 59 patients from the genetic subanalysis, 24 (15.94%) had a genetic mutation (x-linked agammaglobulinemia, 8 cases; severe combined immunodeficiency, 8 cases; hyperimmunoglobulin M syndrome, 3 cases; hyperimmunoglobulin E syndrome, 3 cases; chronic granulomatous disease, 2 cases). We detected 4 novel mutations. No relevant mutations were found in the remaining 35 cases. After treatment with intravenous immunoglobulin and anti-infectious agents, 16 patients died in hospital, and 5 cases died after discontinuing treatment (mortality, 15.22%).
Conclusions: In recent years, the number of patients with PID has risen gradually in South China. Genetic testing can confirm diagnosis. Since PID seriously affects children's quality of life, it is important to diagnose, treat, and intervene early. We hope our clinical and genetic analyses of children with PID can provide diagnostic guidance for clinicians.

Key words: Primary immunodeficiency. Clinical features. Gene. Chinese.

Resumen

Objetivos: El objetivo de este estudio fue analizar los datos clínicos en 138 casos de pacientes con inmunodeficiencia primaria (IDP) y realizar el diagnóstico genético con el fin de mejorar la capacidad de su diagnóstico para pediatras , especialmente en el sur de China.
Métodos: Se realizó un análisis retrospectivo de pacientes con IDP hospitalizados entre mayo de 1999 y junio del 2012, realizando el estudio genético en 59 casos.
Resultados: En cuanto a los resultado obtenidos comprobamos como las manifestaciones clínicas más frecuentes fueron fiebre e infecciones de repetición, generalmente respiratorias y digestivas. En 138 pacientes estudiados la relación varón: mujer fue 113:25, la edad de comienzo 0-119 meses, la edad de diagnóstico 2-159 meses. En 20 casos (14.49%) había una historia familiar de infecciones recurrentes o de miembros muertos en la infancia por dichas infecciones.
En 48 casos (34.78%) se evidenciaron defectos en la producción de anticuerpos, 45 casos (32.61%) mostraban inmunodeficiencia común combinada, y 45 casos (32.61%) otros síndromes de inmunodeficiencias bien definidas. En 59 casos se realizó estudio genético encontrando en 24 de ellos (15.94%) una clara mutación genética, incluyendo 8 casos con Hipogammaglobulinemia selectiva con déficit de IgA, 8 casos con inmunodeficiencia combinada de células T y B, 3 casos de inmunodeficiencia combinada con aumento de IgM, 3 casos con aumento de IgE, 2 casos con CGD. Se encontraron 4 mutaciones nuevas. El resto de los 35 casos no mostraron mutaciones relevantes. Tras el tratamiento con inmunoglubulinas intravenosas y antibióticos, 16 pacientes fallecieron en el hospital, otros 5 tras el tratamiento, siendo la mortalidad del 15.22%.
Conclusiones: En conclusión, en los últimos años se aprecia una elevacion de la incidencia de pacientes con IDP en el sur de China. El análisis genético confirma el diagnóstico de la enfermedad, que afecta gravemente la calidad de vida de los niños, siendo muy importante su diagnóstico y tratamiento precoz. Los resultados de este estudio pueden guiar el protocolo de estudio de la IDP.

Palabras clave: Inmunodeficiencia primaria. Clínica. Genes. Población. China.

Introduction

Primary immunodeficiency disease (PID) comprises a group of clinical syndromes in which reactions of immunocompetent cells and molecules are infrequent or absent because of genetic disorders. Consequently, the body's ability to resist infection is reduced or nonexistent. The current worldwide incidence of PID is unknown. Local incidence rates vary widely: Hong Kong, 1/8000; United States, 1/1200 [1]; Turkey, 24/100 000 [2]; Australia, 2.82/100 000 (not including asymptomatic immunoglobulin [Ig] A deficiency, IgG subclass deficiency, or complement deficiency) [3]; and Japan and Sweden, 1/5000 [4,5]. No data are available for Chinese children. Given the continuous improvement in medical knowledge and diagnostic techniques in recent years, PID is increasingly detected both in China and throughout the world. However, given the clinical features of repeated and chronic infection, which is often complicated by autoimmune diseases and tumors, most patients do not receive treatment from pediatricians specialized in immune diseases. In addition, since many specialists from different areas lack knowledge of this disease, misdiagnosis and delayed treatment are common, thus seriously affecting the prognosis of children with PID in South China. Therefore, in order to strengthen our understanding of this disease, we retrospectively analyzed clinical presentations and genetic features over a 12-year period in South China. Our objective was to improve management of and research into PID in South China.

Methods

Classification and Diagnosis

According to the 2007 International Union of Immunological Societies (IUIS) classification criteria, PID includes the following: T- and B-cell immunodeficiencies; predominantly antibody deficiencies; other well-defined immunodeficiency syndromes; immune dysregulation disease; congenital defects of phagocyte number, function, or both; defects in innate immunity; autoinflammatory disorders; and complement deficiencies [6,7]. These conditions were detected in our clinically diagnosed cases. Given the limitations inherent to genetic testing, we were only able to perform a sequencing analysis in a subset of 59 patients, of whom only 24 had a mutation.

The Institutional Review Board approved the study, and the participants' parents gave their informed consent.

Data Collection

All clinical data were obtained from the medical records of hospitalized patients and outpatients and included age of onset, age at hospitalization, gender, family history, clinical history, onset of symptoms, signs, auxiliary examination, diagnosis, disease progress, and follow-up.

Specimen Collection, Amplification of Relevant Genes, and Gene Sequencing Analysis

Specimens were collected from 59 PID patients during hospitalization between 2009 and 2012. All patients had fasted for 12 to 14 hours. Venous blood (2 mL) was collected in anticoagulant tubes and centrifuged at 3500 rpm for 8 minutes. Plasma was stored at –80°C for DNA extraction. DNA was extracted from 200 μL of blood anticoagulated with EDTA using the QIAamp DNA Blood Mini Kit (Qiagen) in accordance with the manufacturer's instructions. Sequencing was performed using polymerase chain reaction (PCR), which was chosen depending on clinical features and the results of auxiliary examinations.

Statistical Analysis

Data were analyzed using SPSS version 16.0 (SPSS Inc). *P* values of <.05 were considered significant. The χ^2 test was used to determine statistical differences between the groups.

Results

Patients

From 1999 to 2012, we diagnosed (2007 IUIS criteria) 138

Table 1. Onset and Diagnosis of Primary Immunodeficiency

Type	No.	Male/Female	Age at Onset, mo	Age at Diagnosis, mo	Genetic Diagnosis
XLA	36	36/0	12 (0-50)	40 (1-156)	8
Hypogammaglobulinemia	6	0/6	4 (0-119)	8.5 (3-120)	0
Selective IgA deficiency	5	3/2	12 (1-100)	14 (5-108)	0
CD19 defects	1	1/0	1	43	0
SCID	45	39/6	1.3 (0-28)	4 (0.3-85)	8
HIGM	4	3/1	36.5 (9-64)	54 (14-94)	3
Diseases of immune dysregulation	15	9/6	11.5 (0-64)	40 (2-78)	0
HIES	7	4/3	7 (0-12)	49.5 (2-104)	3
WAS	2	2/0	1	2	0
DiGeorge syndrome	1	0/1	3	4	0
Autoinflammatory disorders	4	4/0	2.3 (0-77)	5.7 (1.5-18)	0
Congenital defects of phagocytes	11	5/1	5.5 (0-10)	10 (1.8-108)	0
Chronic granulomatous disease	5	5/0	0.5	21	2
Complement deficiencies	1	1/0	1	12	0

Abbreviations: HIES, hyperimmunoglobulin E syndrome; HIGM, hyperimmunoglobulin M syndrome; Ig, immunoglobulin; SCID, severe combined immunodeficiency; WAS, Wiskott-Aldrich syndrome; XLA, x-linked agammaglobulinemia.

Table 2. Clinical Characteristics and Outcome of Children With PID

Type	Repeated Upper Respiratory Tract Infection	Tympanitis	Pulmonary Infection	Repeated Diarrhea	Bacterial Infection of Skin and Mucous Membrane	Fungal Infection	Arthritis	CNS	TB	Death
XLA	32	14	27	22	4	5	4	3	2	2
Hypogammaglobulinemia	5	0	3	1	0	0	0	0	0	0
Selective IgA deficiency	4	1	2	3	0	0	0	0	0	1
CD19 defects	1	0	1	1	1	1	0	0	0	0
SCID	39	10	31	21	7	25	0	8	0	16
HIGM	2	1	3	0	0	0	1	0	0	0
Diseases of immune dysregulation	12	1	10	8	2	1	0	0	2	0
HIES	6	3	5	0	6	3	0	0	0	0
WAS	1	0	0	0	0	1	0	0	0	0
DiGeorge syndrome	0	0	1	1	0	1	0	0	0	0
Autoinflammatory disorders	2	0	3	3	0	3	1	0	0	1
Congenital defects of phagocytes	5	2	4	1	1	0	0	0	0	1
Chronic granulomatous disease	4	1	5	1	2	2	0	0	1	0
Complement deficiencies	1	0	0	0	0	0	0	0	0	0

Abbreviations: CNS, central nervous system; HIES, hyperimmunoglobulin E syndrome; HIGM, hyperimmunoglobulin M syndrome; Ig, immunoglobulin; SCID, severe combined immunodeficiency; TB, tuberculosis; WAS, Wiskott-Aldrich syndrome; XLA, x-linked agammaglobulinemia.

patients with PID at our institution (male, 113; female, 25; median age at diagnosis, 10 months [range, 2-159 months]). The most common finding was combined immune deficiency and antibody deficiency disease (Table 1). Diagnosis was based on genetic testing in only 24 patients. Median age of onset was 5 months (range, 2 days-119 months); in 63 cases, age at onset was <6 months, in 51 cases it was 6 months to 3 years, and in 24 cases it was >3 years.

Main Clinical Manifestations

In our study population, a positive family history was recorded in 20 cases (14.49%), a previous history of recurrent infections in 94 cases (68.84%), upper respiratory and sinus infections in 116 cases (84.06%), lower respiratory tract infection in 95 cases (68.84%), diarrhea in 63 cases (45.65%), joint swelling and pain in 7 cases (5.07%), tuberculosis after BCG vaccination in 5 cases (3.62%), and seizures in 5 cases (3.62%) (Table 2).

Physical Examination

Physical examination revealed a slower growth rate compared to standard values in 44 cases (31.88%), rash in 50 cases (36.23%), subcutaneous abscess in 11 cases (7.97%), thrush in 40 cases (28.99%), enlarged lymph nodes in 42 cases (30.43%), hepatomegaly in 46 cases (33.33%), and splenomegaly in 32 cases (23.19%).

Laboratory Tests

Various types of PID have specific laboratory characteristics (Table 3). We detected microbial infections in 54 cases (39.13%). These included *Candida albicans* (39 cases), followed by *Klebsiella pneumoniae*, *Staphylococcus aureus*, adenovirus, cytomegalovirus, and herpes simplex virus. Of the 59 patients who underwent genetic testing, 24 had a clear genetic diagnosis, and no mutations were found in the other 35 cases. We detected 4 novel mutations (Table 4).

Table 3. Laboratory Characteristics

Type	No.	Serum Immunoglobulin	T/B/NK Cells[a]	Test
Predominantly antibody deficiencies (XLA, hypogammaglobulinemia, selective IgA deficiency, CD19 defects)	48	Markedly decreased serum Ig including IgG, IgA, IgM Low IgG: 44 cases (too low to measure in 4 cases) Low IgA: 47 cases (too low to measure in 5 cases) Low IgM: 40 cases	Markedly decreased circulating B cells and/or NK cells $CD19^+/CD45^+$, 0%-1%: 36 cases High $CD3^+/CD45^+$: 28 cases Normal $CD3^+CD4^+/CD45^+$:48 cases High $CD3^+$ $CD8^+/CD45^+$: 18 cases	Most of the cases have increased WBC, 47 cases with high ESR, 44 cases with high CRP, 41 cases with low Hb
Combined T- and B-cell immunodeficiencies (SCID)	45	Decreased serum immunoglobulin including IgG, IgA, IgM decreased IgG: 15 cases decreased IgA: 23 cases decreased IgM: 14 cases	Low $CD16^+56^+/CD45^+$: 19 cases Markedly decreased circulating T cells, circulating B cells normal or increased. $CD3^+/CD45^+$: most fluctuated between 0% and 50%, 0% in 14 cases, 1%-10% in 18 cases, 10%-50% in 11 cases	WBC fluctuated between 1 and 4.6×10^9/L for 31 cases, markedly decreased Hb (<90 g/L) in 28 cases, markedly decreased platelet count ($<30 \times 10^9$/L) in 17 cases, increased hs-CRP and ESR in 349 cases

Table 3. Continued

Type	No.	Serum Immunoglobulin	T/B/NK Cellsa	Test
			$CD3^+CD4^+/CD45^+$: most fluctuated between 0% and 30%, 0% in 21 cases, 1%-10% in 14 cases, 10%-30% in 4 cases $CD3^+CD8^+/CD45^+$: most fluctuated between 0% and 13%, 0% in 17 cases, 1%-13% in 17 cases $CD19^+/CD45^+$: fluctuated between 0% and 5% in 3 cases, 18%-92% for 31 cases $CD16^+56^+/CD45^+$: fluctuated between 1% and 7% in 8 cases, 0% in 3 cases, >40% in 1 cases	
Combined T- and B-cell immunodeficiencies (HIGM)	4	IgM increased or normal, IgG and IgA decreased or normal	Circulating T cells, B cells, and NK cells normal or decreased	Different degrees of neutropenia, thrombocytopenia and anemia
Diseases of immune dysregulation	15	No specific rules, some have increased IgE	Imbalance of $CD4^+$ and $CD8^+$	Increased WBC and ESR or CRP when infect
Other well-defined immunodeficiency syndromes (HIES)	7	Markedly increased IgE, fluctuated between 1600 and 31 900 IU/mL, IgA, IgG almost normal	Circulating T cells normal, decreased or normal circulating B cells and NK cells	Increased WBC, eosinophils, and ESR
Other well-defined immunodeficiency syndromes (WAS)	2	Normal IgG, IgA, and IgM and increased IgE	Decreased circulating T cells, and increased B cells	Thrombocytopenia with small platelets
Other well-defined immunodeficiency syndromes (DiGeorge syndrome)	1	Normal IgG, IgA, and IgM	Almost no circulating T cells and increased circulating B cells $CD3^+/CD45^+$: 0%, $CD3^+$ $CD4^+$: 0% $CD3^+CD8^+$: 0%, $CD19^+$: 64% $CD16^+$ 56^+: 26%	Increased WBC, low parathyrin, low calcium (fluctuated between 0.58 and 1.34 mmol/L), CRP: 0.00
Autoinflammatory disorders	4	Partly increased serum IgA, normal or fluctuated IgG and IgE	No specific findings	Increased WBC, ESR
Congenital defects of phagocyte (Chronic granulomatous disease)	11	No specific rules. Some cases have different low level of IgA, or IgG, or IgM	No specific findings	Increased WBC, ESR
Complement deficiencies	1	Low level of C3	Normal circulating T cells and B cells	Increased WBC, ESR

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; HIES, hyperimmunoglobulin E syndrome; hsCRP, high-sensitivity CRP; Ig, immunoglobulin; WAS, Wiskott Aldrich syndrome; WBC, white blood cells.
[a]CD series reference ranges: $CD3^+/CD45^+$, 50%-84%; $CD3^+CD4^+$, 30%-60%; $CD3^+CD8^+$, 13%-41%; $CD19^+$, 5%-18%; $CD16^+56^+$, 7%-40%.

Table 4. Data on 24 Children With Primary Immunodeficiency (Genetic Diagnosis)

Type	Number	Gender	Age at Onset, mo	Age at Diagnosis, mo	Family History	Gene Mutations
XLA	1	Male	60	90	Positive, mother is a carrier	*BTK*, IVS11+1G>A
	2	Male	75	128	Negative, mother is a carrier	*BTK*, IVS17+5G>A
	3	Male	12	40	Positive	*BTK*, exon11, 1036G>A
	4	Male	96	120	Negative	*BTK*, exon12, 1132T>G
	5	Male	28	40	Negative	*BTK*, exon15, 1665C>A
	6	Male	18	20	Negative, mother is a carrier	*BTK*, exon17, 1817G>C
	7[a]	Male	12	67	Negative	*BTK*, exon14, 1396A>T
	8[a]	Male	24	101	Negative	BTK, exon15,1484-1493del

Table 4. Continued

Type	Number	Gender	Age at Onset, mo	Age at Diagnosis, mo	Family History	Gene Mutations
SCID	9	Male	1	5	Negative, mother is a carrier	*IL2RG*, exon6, 868G>A
	10	Male	2	4	Positive, mother and aunt are carriers	*IL2RG*, exon5, 736G>T
	11	Male	0.5	3	Negative	*IL2RG*, exon3, 390C>T
	12	Male	2	4	Negative	*IL2RG*, IVS6+5G>A
	13	Male	2	5	Positive, mother is a carrier	*IL2RG*, exon6, 868G>A
	14[a]	Male	2	3	Negative	*IL2RG*, IVS6-2A>C
	15	Male	2	3	Negative	*IL2RG*, exon2, 216G>A
	16	Male	2	3	Negative	*IL2RG*, exon5, 690C>T
HIGM	17	Male	6	84	Negative	*CD40L*, exon2, 213-216del
	18	Male	8	23	Positive, mother and sister are carriers	*CD40L*, exon5, 655del
	19[a]	Male	6	108	Negative	*CD40L*, from intron 2 to exon3, IVS2-28 to c.358del42
HIES	20	Male	0	96	Negative	*STAT3*, exon13, 1145G>A
	21	Female	2	24	Negative	*STAT3*, exon12, 1121A>G
	22	Male	60	132	Negative	*STAT3*, exon22,2132T>C
CGD	23	Male	0.5	3	Positive, mother is a carrier	*CYBB*, exon8, 871-881del
	24	Male	0	84	Positive, mother is a carrier	*CYBB*, exon2, 91-92del

Abbreviations: CGD, chronic granulomatous disease; HIES, hyperimmunoglobulin E syndrome; HIGM, hyperimmunoglobulin M syndrome; Ig, immunoglobulin; SCID, severe combined immunodeficiency; XLA, x-linked agammaglobulinemia.
[a]Novel mutations.

Outcomes

A total of 21 patients died (15.22%). Of these, 16 died during hospitalization (pulmonary hemorrhage, 1; sepsis, 1; acute respiratory distress syndrome, 4; disseminated intravascular coagulation, 2; and multiple organ failure, 8). The immunodeficiencies of these patients at the time of death were as follows: severe combined immunodeficiency (SCID), 11; x-linked agammaglobulinemia (XLA), 2; selective IgA deficiency, 1; phagocyte defects, 1; autoimmune syndrome, 1). Before October 2008, 72 cases were lost to follow-up. Of the remaining 66 patients, 5 died after giving up treatment (all with SCID). The remaining patients are receiving intravenous immunoglobulin (IVIG), anti-infective drugs, and symptomatic treatment. The mean age at onset differed significantly between the groups (SCID, 1.6 months; XLA, 40.6 months) ($P<.05$). Mortality also differed significantly (35.5% in SCID, 5.55% in XLA) ($P<.05$).

Discussion

Our results provide clinical and genetic data from children with PID in South China over a 12-year period. We hope they increase clinician's understanding of the disease and thus facilitate prognosis and early treatment.

Children with PID and recurrent infections usually have a poor quality of life, and some die during infancy. Therefore, it is important to diagnose the disease and begin treatment early. According to Modell et al [8], the incidence of PID varies with the type of disease: Ig defects (IgA, IgG, IgM) alone or antibody defects accounted for 50% of cases, cellular immune deficiency for 10%, combined immunodeficiency for 20%, phagocyte deficiency for 18%, and complement defects for 2% [8]. Our findings differed from these results, partly because of differences in race and incidence. Since current registration systems are not population-based but case-based, the true incidence rate of PID could be greater than currently reported. The number of new PID patients per year is 2500, which is very high for a developing country such as China.

In our study, 14% to 49% of patients had a positive family history; this finding is close to those recorded in the United States (17%) in 2007 [9]. The male-to-female ratio was 4.52:1, and cases with an age of onset of <6 months accounted for 45.65%. In the United States survey, male patients accounted for 58% and female patients accounted for 38% (4% unknown); patients aged 0-6 years accounted for only 6%, and those aged more than 18 years for 74%. The reasons for the differences recorded in this group could include differences in disease spectrum and racial differences.

Repeated and chronic infection is a key feature of PID. Some children have gastrointestinal and hepatic manifestations [10]. Analysis of a large sample of cases of PID in the United States in 2007 showed that before diagnosis, 90% of patients had recurrent chronic infection and 59% of patients had chronic diseases, the most common being asthma (16.2%), followed by arthritis and sinus infection [9]. A history of recurrent infections before diagnosis was recorded for 68.12% of cases, which is similar in our group, mainly fever, upper respiratory tract and sinus infections, lower respiratory tract infections, gastrointestinal infections, and skin infections. Systemic spread after BCG vaccination was detected in some children:

chronic granulomatous disease was diagnosed in 2 children with tuberculosis (one of whom contracted tuberculosis from his brother). Thus, children with PID are often treated in the respiratory or digestive department, although some may be referred to the neurology, allergy, or rheumatology department. Our data showed that 31.88% of PID patients had growth retardation, thus leaving them more susceptible to viral infections and malignancies [11] and complicating prognosis.

Medical treatment of PID depends to a large extent on prognosis. At present, most children with PID only receive symptomatic treatment, and very few children undergo transplantation. Therapy with IVIG is effective for 83% of children with PID [9]. In our study, we also found that IgG levels increased after IVIG in most children, and some even reached normal levels. However, owing to inefficient evaluation of the disease and administration of IVIG, many children only had limited treatment. Lack of knowledge led directly to seriously delays in diagnosis and treatment, often with tragic results. Therefore, it is especially important to improve pediatricians' knowledge of PID [12].

Long-term survival of patients with SCID who undergo stem cell transplantation is more than 90% [13], although the source of the stem cells and the difficulty involved in matching are problematic. At present, 2 of the patients in our group are being prepared for stem cell transplantation. Our intention is to follow these patients to verify the effectiveness of this approach in China. Clinical trials show that gene therapy constitutes a viable alternative to hematopoietic stem cell transplantation [14]. In addition, studies have shown the therapeutic potential of cytokines in immunodeficiency disease [15].

Improved technology, the rapid development of molecular biology, and increased clinician knowledge facilitate diagnosis of PID [16]. We performed gene sequencing in 59 patients, and a genetic diagnosis was clearly established in 24 (15.94%). No relevant mutations were found in the remaining 35 cases. We detected 4 novel mutations. We also demonstrated the clinical characteristics and new mutations for PID researchers. However, further work is necessary to increase our low level of detection (15.94%).

In summary, in order to enhance the overall understanding of PID for the community and clinicians, it is not only necessary to recognize and diagnose the disease early, but also to improve the level of treatment (and therefore prognosis) and ensure more exhaustive follow-up.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

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