Serum Biomarkers for Early Diagnosis of Chinese X-CGD Children: Case Reports and a Literature Review*

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Summary: Since X-linked chronic granulomatosis disease (X-CGD) exhibits no specific clinical symptoms at an early stage, early diagnosis is difficult and depends predominantly on neonatal screening. Therefore, the aim of this study was to explore routine biomarkers for X-CGD in children and provide clues for early diagnosis. The cases of 10 children with X-CGD diagnosed at Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology from 2013 to 2016 and 122 Chinese children with X-CGD reported in the literature were summarized. Serum biomarkers and clinical symptoms at acute infection were organized. A total of 132 children with X-CGD were enrolled in this study. For 55.8% of the patients, the diagnosis was delayed more than one year after the onset of the first symptoms because no typical clinical symptoms manifested. Children with X-CGD at an acute infection stage showed three recurrent signs in terms of serum biomarkers: (1) the total number of white blood cells (especially N%) was increased significantly, accompanied by anemia in some cases; (2) C-reactive protein (CRP) levels were increased significantly; and (3) most of the patients exhibited very high serum IgG levels (>12 g/L). Diagnosis of X-CGD at an early age is difficult because of its nonspecific clinical features. Our study suggested children with X-CGD suffering acute infection show increases in three typical serum biomarkers, which can provide clues for early diagnosis.
Key words: children; clinical features; early diagnosis; serum biomarkers; X-linked chronic granulomatosis disease

Chronic granulomatous disease (CGD) is a rare inherited paradigm for primary immunodeficiency (PID), characterized by defects in phagocytes. The incidence of CGD has been estimated at between 1 in 200 000 and 1 in 250 000 live births in the USA[1]. The pathogenesis of CGD is due to functional defects in the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex in phagocytes, resulting in loss of the ability to produce the superoxide anions and hydrogen peroxide necessary for killing peroxidase-positive bacteria and fungi[2]. X-linked chronic granulomatosis disease (X-CGD), caused by CYBB gene mutation, is the most common form of CGD, accounting for 65% of all male patients[3]. The age of first onset for 2/3 of children with this disease is very early, even in the neonatal period[4]. Early diagnosis is difficult because of scarce specific clinical manifestations. In some countries, patients are diagnosed early through neonatal screening. However, in many other countries, including China, neonatal screening does not cover this disease, resulting in a lack of early diagnosis and treatment. Special examinations required for the diagnosis of X-CDG, such as DHR flow cytometric assays, can only be carried out at a few domestic hospitals, and gene mutation tests take a long time to complete[5]. Therefore, patients usually suffer from multiple systemic infections, including life-threatening infections, when they are diagnosed. As most studies on X-CDG have been based on case reports and have focused on gene mutations and because the clinical symptoms of the disease largely depend on the type of vaccine injection[6], its clinical features and biomarkers need to be analyzed systematically in different races or countries, due to neonatal screening and vaccine history. With the aim of obtaining evidence allowing early diagnosis of the disease, we summarized the clinical features of 10 children diagnosed with X-CDG

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at our hospital, then combined the results with data from the literature and summarized the clinical features and serological characteristics of children with X-CGD.

1 MATERIALS AND METHODS

1.1 Patients and Clinical Data

A total of 10 children diagnosed with X-CGD were enrolled from 2013 to 2016. Clinical data, including the age of first onset, age at diagnosis, systems infected at onset and at diagnosis and serum biomarkers (e.g., peripheral blood cell counting, CRP, serum immunoglobulin levels), were retrospectively collected. The age at onset was defined as the age when obvious infections initially occurred in the patients. The age at diagnosis was defined as the age when CYBB gene mutations were identified, or respiratory burst activation in neutrophils was detected. Serum biomarkers were obtained from the data for patients suffering acute infections. This study was conducted in accordance with the declaration of Helsinki and was approved by the Medical Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology.

1.2 Literature Search

The clinical literature, primarily including case reports published up to December 2017, was searched at the Wanfang database, CNKI database and PubMed database using "chronic granulomatosis disease" or "X-linked chronic granulomatosis disease" as search terms. We focused on the literature from mainland China that included clinical features and serum markers. All of the data were combined and analyzed.

2 RESULTS

2.1 X-CGD Patients Show Obvious Lag Time between the Age at Onset and Diagnosis

Clinical data from 10 cases of X-CGD in our hospital are presented in table 1. We searched all of

Table 1 Clinical data from 10 children with X-CGD diagnosed in our hospital

No.	Age at onset	Age at diagnosis	Systems involved at onset	Systems involved when diagnosed	WBC ($\times10^9$/L)	N%	HB ($\times10^{12}$ g/L)	IgG (g/L)	CRP (mg/L)
1	2 months	4 months	Pneumonia, urinary tract infection, congenital heart disease, gastric turnover, liver dysfunction	Chronic granulomatosis, sepsis, congenital heart disease	21.6	48.3	106	10.2	74.4
2	3 months	2 years and 11 months	Liver abscess	Severe pneumonia, fungal pneumonia, chronic granulomatosis	16.21	71.6	91	11.2	145.7
3	Newborn	2 years and 8 months	Neonatal pneumonia	Persistent bronchial pneumonia, ulcerative stomatitis, sepsis, electrolyte disorder, anemia, chronic granulomatosis	12.71	63.2	100	12.5	62.9
4	3 months	3 months and 10 days	Sepsis, neck cysts with infection, bronchial pneumonia, left axillary lymph node tuberculosis	Septicemia, neck cysts with infection, bronchial pneumonia, lymph node tuberculosis, mild anemia	23.5	64.4	102	12	76.5
5	2 years and 8 months	2 years and 8 months	Sepsis, severe pneumonia	Sepsis, severe fungal pneumonia, hypoalbuminemia	20.88	65.6	92	18.3	94.8
6	3 months	1 year and 10 months	Lymph node tuberculosis	Bilateral lung infection, acute suppurative tonsillitis, liver dysfunction, lymph node tuberculosis	13.51	51.1	106	19.63	56
7	Newborn	1 year and 4 months	Neonatal pneumonia	Acute bronchial pneumonia	17.13	51.7	77	26.2	78.3
8	Within 1 year old	3 years and 2 months	Lymph node tuberculosis	Severe pneumonia, fungal pneumonia, lung abscess, sepsis, tuberculosis, lymph node tuberculosis, liver dysfunction, anemia, coagulation, dysfunction, electrolyte imbalance	25.27	84.8	93	16.8	208.6
9	2 months	3 months and 16 days	Sepsis, sepsis-related encephalopathy, infectious intestinal obstruction, perianal abscess	Sepsis, pneumonia, perianal abscess, diarrheal disease, moderate anemia	7.82	61.0	100	18.6	0.9
10	Newborn	2 years and 8 months	Antifeedant	Pneumonia	11.59	51.5	73	19.1	151.3

WBC: white blood cell; N%: percentage of neutrophils; HB: hemoglobin; CRP: C-reactive protein

the published literature, including case reports. After removal of duplicates and further analysis to remove cases without clinical manifestations and/or serum features, we obtained a total of 22 articles, including 122 cases, as listed in table 2. A total of 132 cases were enrolled in this study, among which 95 cases had a clear age of onset and diagnosis. Most children suffered the first symptoms of X-CGD at an early age but were diagnosed late, as shown in fig. 1A. The median age of onset was one month (ranging from newborn to 3.5 years). Among the 95 cases, 80 patients (84.2%) were admitted to doctors within 3 months of birth, 42 of whom (44.2%) experienced an attack during the neonatal period, while only 10 (10.5%) children had an age of onset older than 1 year. The median age of diagnosis was 18 months (ranging from newborn to 15 years). There were only 23 (24.2%) cases that were diagnosed within 3 months of birth; most of these patients came from Beijing, Shanghai, Wuhan, and Chongqing and from other first-line hospitals with pioneering pediatricians. The median duration from onset to diagnosis was 14 months (range 0–13 years), with only 30 (31.6%) cases being diagnosed within 3 months after onset. In most children (53/95, 55.8%), the time from onset to diagnosis was more than one year. Before diagnosis, the children were often hospitalized many times due to recurrent infections, as shown in fig. 1B.

Table 2 Reports from the literature included in this study

No.	Total number of patients	First author	Reference source
1	2	Xiaoxu Yang	[7]
2	1	Zhenzhou Long	[8]
3	1	Changling Ge	[9]
4	2	Jianxin He	[10]
5	1	Xi Lu	[11]
6	3	Baoying Zheng	[12]
7	1	Manji Qin	[13]
8	1	Haiyan Liu	[14]
9	4	Hailan Wu	[15]
10	1	Huijun Huang	[16]
11	2	Zixin Yang	[17]
12	1	Jun Yang	[18]
13	12	Shujuan Li	[19]
14	1	Yungen Qian	[20]
15	1	Yuanyuan Xiao	[21]
16	1	Zhanjie Cui	[22]
17	1	Xiaoqing LI	[23]
18	2	Jianxin He	[24]
19	3	Jianxin He	[25]
20	1	Wenli Zhao	[26]
21	38	Huang Xu	[27]
22	42	Jing Wu	[28]

2.2 Additional Organs Are Infected between the Age at Onset and Diagnosis

The children with X-CGD included in our cohort suffered infections at an early age, but their early clinical symptoms were atypical (fig. 2A). Among the 35 cases with clear clinical records, there were 17 cases of pneumonia (48.6%), 8 cases of skin abscess (22.9%), 7 cases of sepsis (20%) and 6 cases of perianal abscess (17.1%), which were the most common onset symptoms. As these symptoms also occur among normal infants, it is difficult to obtain clues from them for the early diagnosis of X-CGD. Some unusual diseases recorded in infants and young children, such as lymphonodus tuberculosis (6 cases, 17.1%), lung tuberculosis (2 cases, 5.7%) and liver abscess (1 case, 2.9%), might provide clues for early diagnosis, but the incidence of these diseases at onset was quite low.

When X-CGD is diagnosed, infections are observed in multiple systems and can even be life threatening (fig. 2B). Among the 90 cases with a definite diagnosis (10 cases from our hospital, 80 cases from the literature), the most common disease (72 cases, 80%) was pneumonia, including rare fungal pneumonia, followed by skin abscess (30 cases, 33.3%), lymphonodus tuberculosis (25 cases, 27.8%), lung tuberculosis (22 cases, 24.4%) and perianal abscess (21 cases, 23.3%). Some children even exhibited serious life-threatening diseases, such as purulent meningitis (5 cases, 5.6%) and liver abscess (7 cases, 7.8%).

2.3 Characteristics of Serum Biomarkers in Children during Acute Infection

Based on the summarization of our clinical cases, combined with data on the features of cases reported in the literature, we found that children with X-CGD

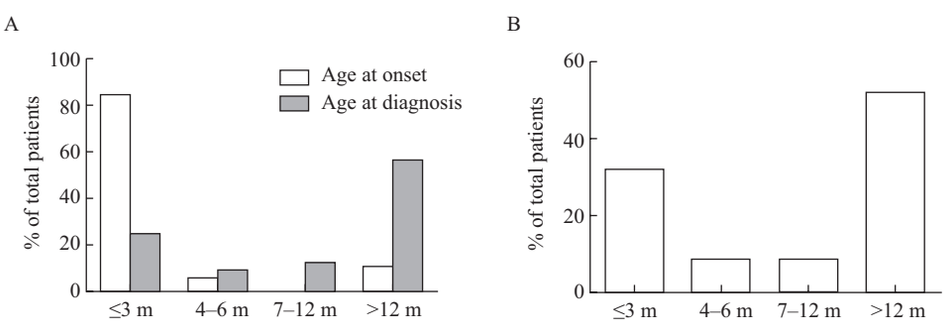

Fig. 1 Distribution diagrams of age at onset and diagnosis (A) and the time lag from onset to diagnosis (B)
m: months

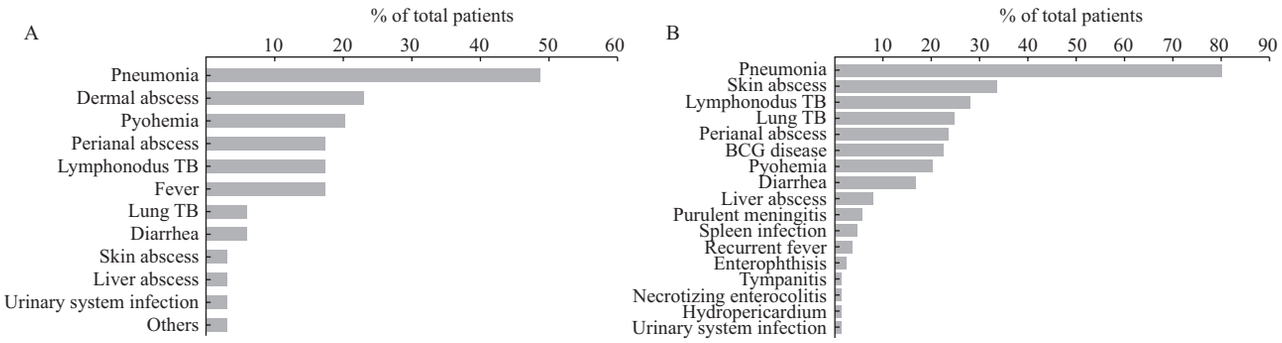

Fig. 2 Diseases from which X-CGD children suffer at onset and diagnosis
A: Diseases from which X-CGD children suffer at onset; B: Diseases from which X-CGD children suffer at diagnosis

presented the below characteristics during acute infection, as shown in table 3, which may provide clues for early diagnosis. We identified three serum biomarkers.

Table 3 Statistics of three serum biomarker signs in children with X-CGD

Name	Total number of cases	Classification	No. of cases	% of total patients
WBC ($\times 10^9$/L)	87	>10	81	93.1
		>15	53	60.9
CRP (mg/L)	31	Increased	30	96.7
		>50	26	83.8
IgG (g/L)	78	>12	42	53.1

2.4 The Total Number of White Blood Cells, Especially Neutrophils, Is Significantly Increased, Accompanied By Anemia

Among the 132 children with X-CGD, there were 87 cases in which the counts of white blood cells were recorded, 81 of whom (93.1%) showed an increase in the total number of white blood cells (>10×10^9/L), especially regarding the percentage of neutrophils. There were 53 cases with a total white blood cell count greater than 15×10^9/L, accounting for 60.9% of all children and 65.4% of children showing an increase in the total number of white blood cells. The higher total white blood cell counts were accompanied by anemia in most children. According to medical records, 21 of 23 cases exhibited some degree of anemia, accounting for 91.3% of the patients. Eight of the 10 cases in our hospital showed slight anemia, whereas the other 2 cases presented moderate anemia, manifested by small cell hypochromic anemia.

2.5 During Acute Infection, CRP Is Increased Dramatically

In addition to greater white blood cell counts, children with X-CGD suffering acute infections showed dramatically increased CRP. For 31 cases, there was a record of CRP and 30 of these cases (96.7%) showed an increased CRP, with 26 cases (83.8%) exhibiting CRP greater than 50 mg/L. Based on our data, 9 of 10 cases displayed an increased CRP.

2.6 High levels of IgG

Children with X-CGD suffering acute infections showed abnormally high IgG levels. Among the 10 children diagnosed at our hospital, 8 (80%) showed elevated serum IgG levels. In the examined literature, blood IgG levels were recorded for a total of 78 patients, 42 (53.1%) of whom showed significantly increased IgG levels (>12 g/L).

3 DISCUSSION

X-CGD is the most common clinical type of CGD. Most children with X-CGD experience at least once serious infection in the first year after birth, with pneumonia being the most common. Diagnosis of CGD at an early age is difficult because of its nonspecific clinical features[29]. In most developed countries, earlier diagnosis depends on neonatal screening. In China and many developing countries, neonatal screening of primary immunodeficiency diseases has not yet been implemented, and clinicians lack knowledge of the early status of CGD, which are two important factors responsible for the delay in diagnosis. Clinicians usually do not have a sufficient understanding of CGD at the early stage, which leads to delayed diagnosis. The median age at onset was 1 month and the median age at diagnosis was 1.5 years, but the children diagnosed within 3 months after first suffering from the disease accounted for only 24.2% of the total cohort. Most of these children receiving an early diagnosis came from the regions and hospitals with relatively good comprehensive medical resources. This situation is directly related to the doctor's ability to diagnose the disease early, which mainly relies on the respiratory burst test. Currently, this test is largely available only in developed areas, which is another important factor in the early diagnosis of these children. Genetic diagnosis is an important tool for diagnosing X-CGD but requires

more time. The current data suggest that the median time between onset and diagnosis is 14 months, which means that it takes more than one year for most children to receive a clear diagnosis. During this time, children are often hospitalized many times due to repeated infections. Genetic diagnosis is somewhat helpful in diagnosis and type differentiation, but no specific mutation hotspots in Chinese population have been identified. One report indicates that only 78.9% of children with CGD have been diagnosed in the past five years[27]. Therefore, there is an urgent need to increase the clinician's understanding of this disease at an early age. CGD is a primary immunodeficiency disease, and early vaccination can lead to vaccine-related diseases[6]. In Europe and the United States, primary immunodeficiency diseases are included in neonatal screening, but such screening is currently not performed routinely in China. Children with X-CGD show certain common diseases in infants and young children in general, making it difficult to consider the diagnosis at an early age according to clinical symptoms alone. Nevertheless, some unusual symptoms observed in infants and young children, such as tuberculosis, lymph node tuberculosis and liver abscess, could provide clues for early diagnosis, although they are rare as first symptoms and might not sufficiently trigger the attention of clinicians to contribute to effective diagnosis. Therefore, children with X-CGD generally have suffered several infections and shown involvement of multiple systems by the time when the disease is clearly diagnosed. Pneumonia is still the main disease recorded in these children. In the present study, 80% of children were found to present a pulmonary infection, similar to the data from European and American countries. Winkelstein and van den Berg reported the proportion of patients with lung infections to be 79% and 66%, respectively[30, 31]. In contrast, lymph node tuberculosis and tuberculosis occur at relatively high rates among Chinese children, which is significantly different from the findings in European and American countries (0%)[31]. The main reason for this disparity is that China does not yet carry out immunodeficiency disease-related neonatal screening, although Bacillus Calmette-Guerin (BCG) vaccination has been included in the national immunization program. Therefore, children with immunodeficiency will suffer from BCG-related diseases due to BCG vaccination. In general, X-CGD is a possible diagnosis when children exhibit repeated severe infections, such as lymph node tuberculosis and tuberculosis, which are very rare in infants and young children. These infections involve multiple systems and are therefore very difficult to treat effectively. Hence, it is necessary to diagnose the disease at an early age.

Although clinical features at an early age were nonspecific, children with X-CGD suffering acute infection showed three typical signs in terms of serum biomarkers. The combination of these biomarkers and the patients' medical histories provide clues for early diagnosis. Most patients in the acute phase of infection exhibit a significantly increased total white blood cell count, especially for neutrophils (N%). We found that cases whose total white blood cell count was $>10\times10^9$/L accounted for 93.1% of patients, and an elevated N% was found in all patients (100%). The patients who showed a total white blood cell count greater than 15×10^9/L accounted for 60.9% of the total group of children, which corresponded to 65.4% of children whose total white blood cell count was increased. After bacterial or fungal infection, normal phagocytes will engulf bacteria or fungi and trigger a respiratory burst, which eventually clears the original infection. However, children with X-CGD exhibit NADPH oxidase complex dysfunction, and the respiratory burst is therefore damaged, preventing the phagocytes from effectively killing the micro-organisms. As a type of feedback, the bone marrow is stimulated to produce more phagocytes. Therefore, the children suffer from persistently increased blood cell counts, especially those of neutrophils. In addition to the increase in the total white blood cell count, most children also exhibit some degree of anemia. The second serological characteristic of children with X-CGD is that their CRP levels are increased. A significant increase in inflammatory indicators is a significant feature of the acute phase of infection. The third feature is an abnormal increase in blood IgG levels, which was found not only among the 10 children diagnosed at our hospital, but also among the 78 cases whose records were available, among which 42 cases (accounting for 53.1%) exhibited a significantly higher (>12 g/L) level of IgG. In previous studies, it was found that 90% of children with CGD presented high gamma globulin hyperlipidemia[32]. The significantly higher levels of IgG recorded in children who had no history of gamma globulin suggest that the children exhibit immune dysfunction, which is one of the early clues for diagnosing X-CGD. These three serological indicators are not only routine biochemical indicators but are also determined using routine tests for infection that can be carried out in most hospitals.

In summary, the clinical manifestations of children with X-CGD at the age of onset lack specificity, which leads to delayed diagnosis. Our study showed that when patients experience acute infections, they show three typical signs: an increased white blood cell count and dramatically increased CRP and IgG levels, which may provide clues for earlier diagnosis.

Conflict of Interest Statement

The authors declare that they have no potential conflicts of interest regarding this work.

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