Tuberculosis in children with congenital immunodeficiency syndromes

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ÖZET

Konjenital immünyetmezlik sendromu olan çocuklarda tüberküloz

Konjenital immünyetmezlik sendromları olan hastalar, birçok mikroorganizma ile infeksiyona yatkındırlar. Fakat, bu hastalarda nadiren mikobakteriyel hastalık meydana gelir. Bu yazıda, konjenital immünyetmezliği olan ve tüberküloz hastalığı gelişen çocuklardaki klinik, laboratuvar bulgular ve tedavi sonuçları verilmiştir. On hastanın dosyası gözden geçirildi. Üç hastada kronik granülomatöz hastalık, iki hastada sık değişken immünyetmezlik, diğerlerinde siklik nötropeni, kombine immünyetmezlik, hiperimmünglobulin E sendromu, selektif IgA eksikliği ve X'e bağlı agamaglobulinemi vardı. Sekiz hastada pulmoner tüberküloz, birinde tüberküloz artrit, birinde tüberküloz osteomiyelit saptandı. Aside dirençli basil, iki balgam, bir kemik iliği aspirasyonu ve bir postmortem akciğer nekropsi örneğinde tespit edildi. Bir balgam ve bir eklem sıvısı aspirasyonunda Mycobacterium tuberculosis üretildi. Bir hastaya kemik biyopsisi ile tanı konuldu. Diğer üç hasta, tüberkülin deri testi pozitifliğiyle antibiyotik tedavisine yanıt vermeyen klinik ve radyolojik bulgular nedeniyle tanı aldı. Tüm hastalar antitüberküloz tedavi aldı. Sonuç olarak, Mycobacterium türleri, özellikle endemik bölgelerde yaşayan konjenital immünyetmezliği olan çocuklarda hastalığa yol açan önemli patojenler olabilir.

Anahtar Kelimeler: *Tüberküloz, çocuk, konjenital immünyetmezlik sendromları.*

SUMMARY

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Patients with congenital immunodeficiency (CID) syndromes are susceptible to various microorganisms. However, relatively few CID disorders develop mycobacterial disease. We describe clinical features, laboratory findings and therapeutic outcome of children with CID who had tuberculosis disease. Medical reports of 10 patients were reviewed. Three patients had chronic granulomatous disease, two had common variable immuno deficiency, the others had cyclic neutropenia, combined immunodeficiency, hyperimmunoglobulin E syndrome, selective IgA deficiency and X-linked agammaglobulinemia. Eight patients presented with pulmonary tuberculosis, one had tuberculosis arthritis, one had tuberculosis osteomyelitis. There was acid fast bacilli in sputum of two, bone marrow aspiration in one and postmortem lung biopsy specimen in one patient. Mycobacterium tuberculosis grew in sputum of one and articular fluid aspirate of one patient. One patient was diagnosed with bone biopsy specimens characteristic for tuberculosis. The remaining three patients were diagnosed to have tuberculosis disease as they had positive tuberculin skin test and clinical and radiologic findings unresponsive to nonspecific treatment. All patients were treated with antituberculous drugs. Mycobacterium species may be important pathogenes in children with CID, especially in endemic regions.

Key Words: *Tuberculosis, children, congenital immunodeficiency syndrome.*

Tuberculosis continues to be a major cause of morbidity and mortality. The number of tuberculosis cases has increased dramatically over the last decade. An estimated one-third of the world's population (2 billion people) is infected with the tubercule bacilli. The incidence of tuberculosis in Turey in 2007 was 27 in 100.000 (1). Patients with immunocompromising diseases are at high risk for infection and disease with *Mycobacterium* species. Congenital immunodeficiency (CID) syndromes are inherited defects of the development or function of one or more components of the immune system (2). The impact of each genetic disorder is highly variable ranging from rapidly lethal if bone marrow transplant is not performed like severe combined immunodeficiency syndrome from asymptomatic like most patients with selective IgA defects. So, CID syndromes are susceptible to various microorganisms like viral, bacterial, fungal or protozoal with different degrees of severity. However, relatively few CID disorders develop mycobacterial disease. Besides, it is not clear which patients with CID have disseminated mycobacterial disease following vaccination with BCG or have non-tuberculous mycobacteria or *Mycobacterium tuberculosis* disease (2). There is little data available about this issue consisting of few published cases, so in this retrospective study we aimed to describe the clinical features, course, the laboratory findings and the therapeutic outcome of children with different CID syndromes who had tuberculosis disease.

MATERIALS and METHODS

Ten children with CID who were diagnosed with tuberculosis disease were included in this study. Patients who had genetic susceptibility to mycobacterial infections like defects of the interleukin-12 interferon-gamma axis were excluded. The medical reports of patients were reviewed to evaluate the clinical features, the course of the disease, the laboratory findings and the therapeutic outcome. Tuberculosis was diagnosed with microbiologic tests or pathological examination of tissues or with clinical and radiologic findings consistent with tuberculosis. The tuberculin skin test (TST) was administered by injecting five tuberculin units of purified protein derivative on the volar aspect of the forearm (Mantoux test). An induration of 15 mm and greater was considered to be positive and was negative if less than 15 mm as all patients were vaccinated with BCG vaccine. In all patients, specimens from one or more of the following sites were cultured for *M. tuberculosis*: Sputum, gastric aspirates, lung, bone or snovia. This was a retrospective study which had no potential to influence patient management. Patient confidentiality was maintained at all times.

RESULTS

Age at diagnosis of tuberculosis ranged between five months and 17 years (median five years) and age at diagnosis of CID ranged between five months and 17 years (median three years). The diagnosis of tuberculosis preceded the diagnosis of CID in two patients, both diseases were diagnosed at the same time in two patients and diagnosis of CID preceded the diagnosis of tuberculosis in the rest of the patients. Three patients had chronic granulomatous disease (CGD), two had common variable immunodeficiency (CVID), the others had cyclic neutropenia, com-

bined immunodeficiency, hyper-IgE syndrome, selective IgA deficiency and X-linked agammaglobulinemia (XLA). There were no exposure to adults with tuberculosis, except two patients (case numbers 1 and 10). All were vaccinated with BCG and TST was positive in only six of them. Eight patients presented with pulmonary tuberculosis, one had tuberculosis arthritis and one had tuberculosis osteomyelitis. Microbiological examinations showed positive acid fast bacilli (AFB) in four patients. *M. tuberculosis* grew in sputum of one patient and articular fluid aspirate of one patient. One patient was diagnosed with bone biopsy specimens characteristic for tuberculosis. Histologic examination of lung lesion in one and ankle snovia in another patient which was consistent with tuberculosis led to the diagnosis. The remaining three patients were diagnosed to have tuberculosis disease as they had positive TST and clinical and radiologic findings unresponsive to non-specific treatment. Clinical, radiological and microbiological findings of patients are shown in Tables 1, 2.

All patients were treated with antituberculous drugs. One died in the begining of the treatment and one was lost to follow up; all the remainder were recovered clinically and radiologically.

DISCUSSION

In this report, we described our cases with CID and tuberculosis. Our patients had different types of CID syndromes. Among those, combined immunodeficiency is primary combined antibody and cellular immunodeficieny. Our patient with combined immunodeficiency had proven tuberculosis with postmortem lung biopsy, which we think is the first published case.

Hyperimmunoglobulin E syndrome is especially characterized by recurrent severe staphylococcal abscesses of the skin, lungs and other viscera with reduced neutrophil chemotaxis, variably impaired T-cell function and highly elevated levels of IgE (3). Primary lung infections are typically due to *Staphylococcus aureus*, *Haemophilus influenzae*, *Pseudomonas aeruginosa* and *Aspergillus fumigatus* (2). Until now, only an adult case with pneumonia due to *Mycobacterium intracellulare* and a nine years-old girl who had disseminated BCG infection have been reported among patients with hyperimmunoglobulin E (4,5). Our hyperimmunoglobulin E is the first published tuberculosis case with positive AFB in sputum who presented with an abscess appereance in chest X-ray.

CGD which is a rare disorder of phagocyte dysfunction is characterized by the ability of neutrophils and monocytes to ingest but their inability to kill catalase-positive microorganisms because of a defect in the generation of microbial oxygen metabolites (6). There are reports on mycobacterial disease in these patients and

Table 1. Clinical characteristics of patients.

Case no	Sex	Age at diagnosis of CID	Age at diagnosis of TB	Consanguinity between parents	History of sibling with CI	CID syndrome
1	Female	4.5 years	2.5 years	+	-	Cyclic neutropenia
2	Female	4 years	4 years	+	+	CGD
3	Female	14 years	6 years	+	-	CGD
4	Female	1.5 years	12 years	+	-	HIE
5	Male	7 years	10 years	-	-	CVID
6	Female	5 months	5 months	+	+	Combined immunodeficiency
7	Male	2.5 years	4 years	+	-	XLA
8	Female	17 years	17 years	+	-	CVID
9	Female	2.5 years	5 years	+	+	CGD
10	Female	3 years	6 years	+	-	Selective IgA deficiency

CID: Congenital immunodeficiency, CGD: Chronic granulomatous disease, HIE: Hyperimmunoglobulin E syndrome, XLA: X-linked agammaglobulinemia, CVID: Common variable immunodeficiency.

Table 2. Clinical, radiological and laboratory findings and prognosis of patients.

Case no	Complaint	Physical examination	TST (mm)	Chest X-ray	TB	Sites of AFB positivity	Sites of recovery of *M. tuberculosis*	Histology consistent with TB	Outcome
1	Fever, night sweat, weight loss	Tubular sound	0	Consolidation	Pulmonary	Bone marrow aspiration	-	-	Recovered
2	Fever, cough	Tubular sound	18	Consolidation	Pulmonary	-	-	-	Recovered
3	Fever, cough	Tubular sound	6	Consolidation	Pulmonary	-	-	-	Recovered
4	Fever, cough	Clubbing	15	Abscess, hilar lymphadenopathy	Pulmonary	Sputum	-	-	Recovered
5	Cough	Crackles	27	Atelectasis	Pulmonary	-	-	-	Recovered
6	Fever, cough	Crackles	0	Bilateral ground glass	Pulmonary	Postmortem lung biopsy	-	Postmortem lung biopsy	Died
7	Swelling and redness in the ankle	Swelling in the ankle	25	Bronchiectasis	Joint	-	Joint fluid aspiration	Ankle snovia	Recovered
8	Cough, sputum	Clubbing	0	Bronchiectasis	Pulmonary	Sputum	Sputum	-	Lost to follow up
9	Fever, cough	Normal	25	Consolidation	Pulmonary	-	-	Lung	Recovered
10	Foot swelling	Swelling in the foot	16	Normal	Bone	-	-	Bone	Recovered

TB: Tuberculosis, TST: Tuberculin skin test, AFB: Acid fast bacilli.

CGD patients appears to be vulnerable to mycobacteria including *M. tuberculosis* in endemic areas (2). We could not isolate the microorganism in our patients with CGD, but lung lesions unresponsive to non-specific antibacterial treatment together with TST positivity led to their tuberculosis diagnosis.

Hypogammaglobulinemia, XLA, CVID, selective IgA deficiency and cyclic neutropenia do not have an increased susceptibility to mycobacteria (2). Abdominal infection due to *Mycobacterium avium-intracellulare* complex was found in an adult patient with CVID and another adult patient with a late onset CVID had pulmonary infection with *M. tuberculosis* (7,8). Other than these two adult patients, our case with CVID is the third reported case who had a proven pulmonary tuberculosis disease. The occurence of tuberculosis in our patients with the above mentioned antibody deficiencies and congenital phagocyte defects like cyclic neutropenia might have been coincidental and not linked to the underlying immunodeficiency.

In general, the diagnosis of tuberculosis in children is difficult and is based on a combination of history of contact with an adult infectious case, clinical symptoms, chest radiograph, TST and microbiological evaluation. The diagnosis of tuberculosis in children with CID is even more challenging, because symptoms and signs are non-specific and both clinical and radiological findings can mimic many other infectious diseases like *Pneumocystis carinii* or other bacterial pneumonia which are common in these diseases. Besides, most patients may have bronchiectasis due to recurrent pneumonias and may present with cough and sputum production which can further delay the diagnosis. On the other

hand, many children with CID can have features of interstitial lung disease, like development of lymphoid interstitial lung disease in CVID, which makes the diagnosis more difficult (9).

From this report, it can be concluded that *Mycobacterium* species may be important pathogenes in children with CID syndromes, especially in endemic regions. A high index of suspicion by the clinician is required in such patients and it should be kept in mind that tuberculosis may be the cause in patients who are unresponsive to non-specific therapy. Early recognition of tuberculosis and appropriate therapy in children with CID syndromes is necessary not only to provide optimal care to patients but also to prevent the spread of the disease to others.

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