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Short Communication

Paradoxical reaction in immunocompetent children with tuberculosis

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SUMMARY

Background: A paradoxical reaction (PR) during anti-tuberculosis treatment is a phenomenon that is poorly studied in immunocompetent children. It is defined as a clinical or radiological worsening of pre-existing tuberculosis (TB) disease.
Methods: A retrospective descriptive study of children younger than 14 years of age was performed; these children developed PR during the years 2009 to 2014, following a diagnosis of TB. Demographic characteristics, microbiological results, treatment and outcome data were collected.
Results: Of 51 children diagnosed with TB, five (9.8%) developed a PR; four of these children had pulmonary TB and the remaining patient had miliary TB with central nervous system involvement. The PR occurred at a median of 42 days (range 23–53 days) after initiating therapy. Corticosteroids were started when PR was suspected, at a median dose of 1 mg/kg/day. Clinical and radiological improvement was noted in all cases, with a median clinical regression time of 10.5 days (range 3–15 days) and a median radiological regression time of 45 days (range 26–105 days). No sequelae were described in any patient.
Conclusions: PR in immunocompetent children during anti-tuberculosis treatment is not such an unusual reaction. Treatment with corticosteroids may be useful for the resolution of PR.

1. Introduction

Patients with tuberculosis (TB) can suffer an unexpected deterioration despite good therapeutic compliance. This phenomenon is known as paradoxical reaction (PR), defined as the clinical or radiological worsening experienced by patients with good adherence to treatment.[1] Such a reaction has been described extensively in HIV-positive patients, i.e. the immune reconstitution inflammatory syndrome (IRIS). Likewise, the emergence of PR has also been observed in the immunocompetent population.[2]

With regard to children, PR has mostly been reported in isolated clinical cases,[3,4] and only two studies have been published to date.[5,6] This article reports the cases of immunocompetent paediatric patients diagnosed with TB who developed PR over a period of 5 years.

2. Patients and methods

A retrospective descriptive study was performed of patients under 14 years of age diagnosed with TB who developed a PR; these patients presented to the study tertiary care hospital during the years 2009 to 2014.

PR was defined as a clinical or radiological worsening of pre-existing TB lesions or the development of new lesions, in a patient who had initiated TB treatment at least 2 weeks before and in whom a clinical improvement had been observed. The diagnosis of the PR was made during outpatient visits. The exclusion of a bacterial or viral infection, poor compliance to treatment, and resistance to the therapeutic drugs used was required for the diagnosis.[1,7]

The time to onset of the PR was considered as the number of days between the initiation of TB treatment and the diagnosis of PR. The time for PR regression was defined as the number of days between the diagnosis of PR and the first signs of clinical or radiological improvement.

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3. Results

During the study period, 51 children were diagnosed with TB disease; none had congenital or acquired immunosuppression. Five of these patients matched the definition of PR (9.8%): four had pulmonary TB and the remaining one had miliary TB with central nervous system involvement. All patients were autochthonous and Caucasian. The characteristics of these patients are detailed in Table 1.

The TB disease was treated with first-line drugs in all cases, and no adverse reaction was observed. The PR occurred at a median of 42 days (range 23–53 days) after the initiation of anti-tuberculosis drugs. The diagnosis was made on the basis of radiological worsening in all cases, as well as clinical deterioration in four cases.

Of those with the pulmonary forms, two required admission at the time of PR and received systemic antibiotics for a suspected associated bacterial infection; there was no improvement after initiating the antibiotics and no microbiological isolation in either case .

The same TB treatment was maintained for all patients, and systemic corticosteroids were administered in every case for an average duration of 46 days (range 23–109 days) at a median dose of 1 mg/kg/day, which was gradually tapered off. A clinical and radiological improvement was noted in all cases following corticosteroid treatment. The median clinical regression time was 10.5 days (range 3–15 days) and the median radiological regression time was 45 days (range 26–105 days). There were no sequelae after treatment completion.

To investigate possible predictors of deterioration, patients who developed PR were compared with those who continued to improve. No statistically significant difference was found for any of the parameters analyzed (Table 2).

4. Discussion

Although PR is poorly described in the paediatric population, Thampi et al. reported an incidence of 14% among 112 children with TB in Canada,[5] and Olive et al. reported an incidence of 10% in 130 patients in Belgium.[6] In the present study, 9.8% of the children with TB developed a PR, consistent with the results of these previous studies.

The pathophysiology of PR in the immunocompetent population remains unclear . It has been proposed that in the initial moments of infection, the bacillus is phagocytosed by lung macrophages; the triggering of a bactericidal reaction is therefore avoided, favouring a certain state of immunosuppression. An increase in production of interleukin 10 (IL-10) and transforming growth factor beta (TGF-β), which induces the apoptosis of T lymphocytes and reduces the production of interferon gamma (IFN-γ) , decreases the recruitment of new macrophages and promotes this level of immunosuppression. After the initiation of treatment, the immune system improves, either as a consequence of the therapy or spontaneously, and this is the main cause of TB worsening .[2,8]

The two previous studies conducted in children analysed the risk factors for developing PR.[5,6] The main risk factors identified were a weight below the 25th percentile, the involvement of more than one site at initial presentation, and the presence of more serious symptoms at diagnosis. Olive et al. also described a lower age at diagnosis as an independent factor.[6] The risk factors analyzed in the present sample were found not to be statistically significant, probably due to the small sample size.

A change in the anti-tuberculosis therapy used, or in the duration of this therapy, is not recommended during the treatment of PR. The use of corticosteroids has been proposed by several authors, with different results obtained.[3,4,6] Although there is no

Table 1
Characteristics of paediatric patients with TB who developed a paradoxical reaction

Patient	TB form	Age, years	Sex	Isolation of *MT*	TB regimen	Radiology at diagnosis	PR onset, days	PR symptoms	PR radiology	PR treatment	Dosage, mg/kg/ day	Steroids duration, days	PR clinical regression, days	PR radiological regression, days
1	Pulmonary	2.3	F	Yes	6 months H,R,Z,E	Parenchymal infiltration in right upper lobe	42	No	Worsening of parenchymal infiltration	Prednisolone	1.5	34	-	38
2	Pulmonary	2.1	M	No[a]	6 months H,R,Z,E	Unknown	50	Fever, cough, and respiratory failure	Hilar adenopathy; right upper lobe infiltration; bronchial compression	Prednisolone	1	109	3	105
3	Pulmonary	2.6	M	Yes	6 months H,R,Z,E	Right paracardiac infiltration	42	Worsening cough	Middle lobe atelectasis	Prednisolone	1.5	33	15	26
4	Pulmonary	1.6	M	Yes	6 months H,R,Z,E	Parenchymal infiltration in right upper lobe (Figure 1)	23	Fever and cough	Right upper and middle lobe atelectasis (Figure 2)	Prednisolone	1	23	6	45
5	Meningitis	7.2	M	Yes	12 months H,R,Z,E	CT chest: miliary pattern Brain MRI: supratentorial and infratentorial tuberculomas	53	Fever recurrence	Increase in number and size of tuberculomas	Prednisone	1	30	15	75

TB, tuberculosis; *MT*, *Mycobacterium tuberculosis*; PR, paradoxical reaction; F, female; M, male; H, isoniazid; R, rifampicin; Z, pyrazinamide; E, ethambutol; CT, computed tomography; MRI, magnetic resonance imaging.
[a] This case was exposed to a confirmed TB case, in which no resistance was observed.