Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Short Communication

Paradoxical reaction in immunocompetent children with tuberculosis

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A R T I C L E   I N F O

S U M M A R Y

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.

Table 2
Baseline characteristics of the patients[a]

	No paradoxical reaction (n = 46)	Paradoxical reaction (n = 5)	p-Value
Median age, years	4.5 (0.1–13.9)	2.6 (1.6–7.2)	0.46
<3 years of age	16 (34.7%)	3 (6.5%)	0.34
Male to female ratio	25/21	3/2	1.00
Weight percentile ≤25%	16 (34.7%)	2 (40%)	1.00
History of TB contact	22 (47.8%)	1 (20%)	0.35
TST median, mm	12	11.5	0.79
Negative	5 (10.8%)	0	1.00
5–14 mm	28 (60.8%)	4 (80%)	0.64
≥15 mm	13 (28.4%)	1 (20%)	1.00
Pulmonary TB	31 (67.3%)	4 (80%)	
Extrapulmonary TB	15 (32.7%)	1 (20%)	1.00
Endobronchial	3	0	
Pleural	2	0	
Disseminated	4	0	
Lymph node	3	0	
Abdominal	1	0	
Meningeal	2	1	
Mycobacterium tuberculosis-positive culture	21 (45.6%)	4 (80%)	0.19
Median lymphocyte count, $\times 10^9$/l	3.120 (0.200–11.900)	3.150 (0.120–5.870)	1.00
Cases with lymphocyte count <1.5 $\times 10^9$/l	5 (10.8%)	1 (20%)	0.42
Median haemoglobin level, g/dl	11.9 (7–13.5)	11.2 (9.3–13.5)	0.76
Median treatment duration, months	6 (6–12)	6 (6–12)	0.83
Number of cases with steroid treatment	6 (13%)	5 (100%)	<0.001

TB, tuberculosis; TST, tuberculin skin test.
  [a] Data are presented as number (%) or median (range). The statistical analysis was done using the Student *t*-test or Mann–Whitney *U*-test for medians and proportions, according to the variable distribution. Categorical variables were compared using Fisher's exact test. The confidence interval was 95%.

clear indication, most authors agree that clinical observation may be sufficient in mild cases and that steroids could be beneficial for severe forms.[2,9,10] With regard to the dose used, most studies have recommended an initial dose of 1 mg/kg/day, with a progressive tapering off over 4 or 6 weeks.[2–4,9]

Corticosteroid treatment was given to all of the patients in this study, with good results. Some of them did not present with a
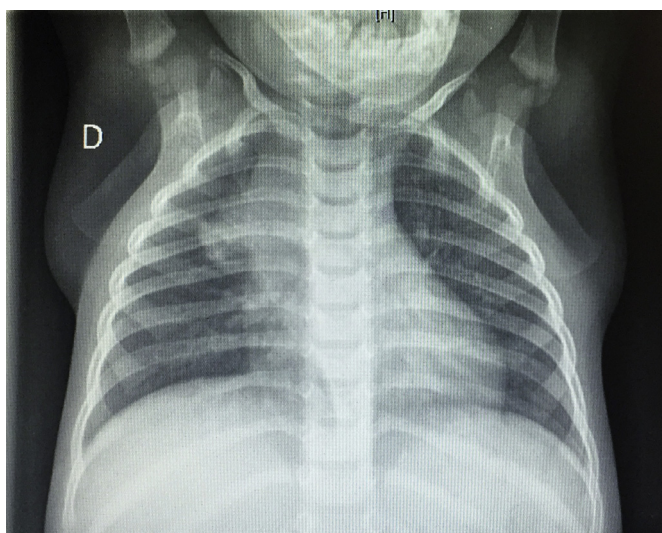

Figure 1. Chest X-ray done at diagnosis of pulmonary tuberculosis in a 2-year-old boy (patient 4, Table 1), showing a right upper lobe infiltration. .
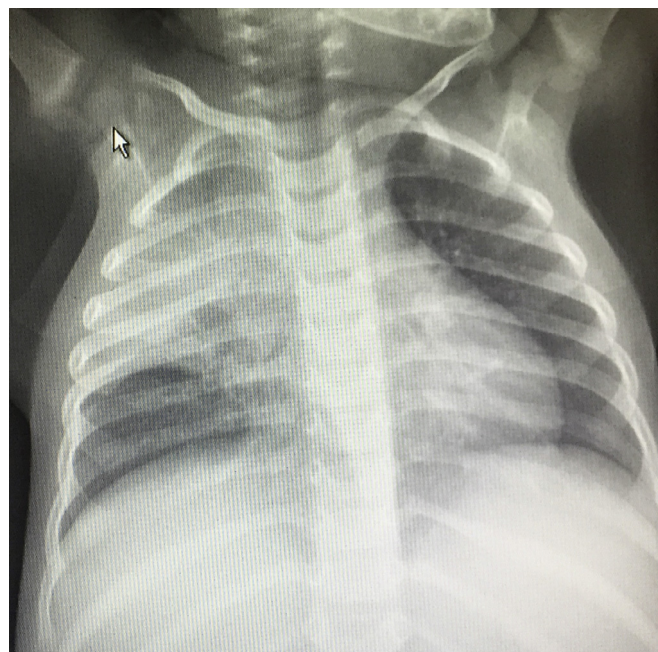

Figure 2. Chest X-ray done in the same patient (patient 4, Table 1) at the time of diagnosis of the paradoxical reaction: a radiological worsening with an increase in parenchymal infiltration and atelectasis in the right upper and middle lobes can be seen.

severe form of PR; therefore, it is possible that their outcomes would have been equally successful without corticosteroid treatment.

This study has several limitations. It was retrospective in design and included a small patient sample. Furthermore, one patient in whom *Mycobacterium tuberculosis* was not isolated was included among those with PR, as the bacillus was isolated in the index case Figures 1 and 2.

In conclusion, PR is not such an unusual occurrence in immunocompetent children with TB. It is important to consider PR when other causes of clinical or radiological worsening have been ruled out.

Funding: None.

Conflict of interest: The authors have no conflicts of interest to report.

References

1. Meintjes G, Lawn SD, Scano F, Maartens G, French MA, Worodria W, et al. Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. *Lancet Infect Dis* 2008;**8**:516–23.
2. Fernández-Fúnez A. Paradoxical response during anti-tuberculosis treatment in immunocompetent patients. *Med Clin (Barc)* 2009;**133**:637–43.
3. Park JA, Park SS, Park SE. A paradoxical reaction during antituberculosis therapy for congenital tuberculosis. *Int J Infect Dis* 2009;**13**:e279–81.
4. Del Rio Camacho G, Jimenéz Jimenéz AB, Górgolas Hernández-Mora M, Sanz Calvo ML, Montoro Chavarrias S, Bernacer Borja M. Paradoxical reaction to tuberculosis treatment in an immunocompetent adolescent. *An Pediatr (Barc)* 2011;**74**:431–3.
5. Thampi N, Stephens D, Rea E, Kitai I. Unexplained deterioration during antituberculosis therapy in children and adolescents: clinical presentation and risk factors. *Pediatr Infect Dis J* 2012;**31**:129–33.
6. Olive C, Mouchet F, Toppet V, Haelterman E, Levy J. Paradoxical reaction during tuberculosis treatment in immunocompetent children: clinical spectrum and risk factors. *Pediatr Infect Dis J* 2013;**32**:446–9.
7. Graham SM, Ahmed T, Amanullah F, Browning R, Cardenas V, Casenghi M, et al. Evaluation of tuberculosis diagnostics in children: 1. Proposed clinical case definitions for classification of intrathoracic tuberculosis diseases. Consensus from an expert panel. *J Infect Dis* 2012;**205**:S199–208.

8. Campbell IA, Dyson AJ. Lymph node tuberculosis: a comparison of various methods of treatment. *Tubercle* 1977;**58**:171–9.

9. Cheng VC, Ho PL, Lee RA, Chan KS, Chan KK, Woo PC, et al. Clinical spectrum of paradoxical deterioration during antituberculosis therapy in non-HIV-infected patients. *Eur J Clin Microbiol Infect Dis* 2002;**21**:803–9.

10. Link-Gelles R, Moultrie H, Sawry S, Murdoch D, Van Rie A. Tuberculosis immune reconstitution inflammatory syndrome in children initiating antiretroviral therapy for HIV infection: a systematic literature review. *Pediatr Infect Dis J* 2014;**33**:499–503.