Paradoxical Response in Patients with CNS Tuberculosis

Meena Gupta*, BK Bajaj**, Geeta Khwaja*

Abstract

Aim: To report paradoxical response, i.e. recurrence of appearance of fresh symptoms, physical and radiological signs in a patient who had previously shown improvement with appropriate anti-tubercular medicines.

Material and Methods: Ten out of 58 patients of CNS tuberculosis, diagnosed on basis of clinical, laboratory and radiological data that initially showed clinical response to therapy only to deteriorate later were included in the study.

Results: Out of ten, three were males and seven were female with age range 13 to 28 years. The duration of time between initiation of therapy and worsening of patient was from one to seven months. Nine out of ten patients developed fresh intracranial tuberculoma while one case otherwise showing improvement developed expansion of tuberculoma and other one of empyema developed tuberculoma while on therapy. All these cases responded to addition of second line therapy or increase in dose of drugs previously prescribed and introduction or increased dose of steroid.

Conclusions: Clinical judgement, regular follow up, guarded reassurance of patient is required to detect parodoxial response in CNS tuberculosis.

INTRODUCTION

Tuberculosis remains one of the common infectious disease of the central nervous system (CNS) in developing countries. Even the developed countries are observing the resurgence of CNS tuberculosis after the appearance of AIDS. Emergence of resistant strains of mycobacteria has made the situation even more complicated. There is now need for even greater acumen in the diagnosis and management of extrapulmonary tuberculosis, particularly CNS tuberculosis. While the most effective and optimum therapeutic regimen for various presentations of CNS tuberculosis is already not well settled, growing problems of secondary resistance, atypical mycobacterial infection and what has come to be known as paradoxical response, have compounded the existing difficulties. Paradoxical response has been defined as recurrence or appearance of fresh symptoms, physical and radiological signs in a patient who had previously shown improvement with appropriate antitubercular medicines. It poses serious problems in the management of CNS tuberculosis. There is always a question of development of drug resistant tuberculosis when there is worsening of the patient and often this leads to inappropriate increment or addition of more toxic newer antitubercular drugs with adverse consequences. We are reporting 10 cases of CNS tuberculosis with paradoxical response to antitubercular therapy (ATT) observed at our centre.

MATERIAL AND METHODS

Our study was a prospective study of patients of CNS tuberculosis who presented at the CNS infection clinic, GB Pant Hospital, New Delhi between 1996 and 2000. We analyzed 58 patients on the basis of adequacy of available data, compliance of medicines and regular follow up. Diagnosis of CNS tuberculosis was made on the basis of clinical, laboratory and radiological information. Patients were subjected to imaging and CSF analysis, wherever and whenever indicated or feasible. All our patients received rifampicin, isoniazid, pyrazinamide, ethambutol/ethionamide/streptomycin in the beginning of therapy. Steroids were given to patients depending on clinical state of the patients and stage of TBM. Duration of steroid therapy was individualized according to clinical circumstances of the patients. We categorized patients into four groups (A, B, C and D) on the basis of type of presentation as below:

Group A: Tubercular meningitis (TBM)
Group B: TBM with associated tuberculoma
Group C: Tuberculoma

Group D: Extracranial tuberculosis

A patient was labeled as a case of paradoxical response to CNS tuberculosis if despite being on antitubercular drugs, the patient worsened after a period of initial improvement. After some drug modification in the form of addition of steroids/fluoroquinolones/ethionamide or increasing the dose of ATT these patients improved subsequently. Whenever there was deterioration in the clinical condition of the patients, repeat imaging and complete CSF analysis as deemed necessary, was undertaken.

RESULTS

Our analysis yielded 10 patients (Male:Female = 3:7; Age range = 13-28 years) who showed paradoxical response. All the patients in the group were diagnosed on the basis of clinical, radiological and CSF findings. The patients with TBM (group A and B), who were subjected to CSF analysis, showed raised proteins, normal to low normal sugar and lymphocytic pleocytosis. In all the cases, CSF analysis failed to reveal AFB/Cryptococcus and, mycobacterial and fungal culture reports were negative. PCR for M. tuberculosis was positive in only one of the seven patients with TBM. Of the seven patients belonging to group A and B, five patients were in stage II and two patients were in stage III of TBM. One patient of extracranial tuberculosis group was shown to have had AFB positive granuloma in pleural biopsy. Paradoxical response developed four weeks to 17 months after the initiation of therapy in the patients. All the patients developed fresh symptoms and signs heralding the paradoxical response except one case in which on routine follow up CT scan, asymptomatic new tuberculomas were seen. Of all the 10 patients, three developed paradoxical response while steroid dose was being lowered and four patients developed the response when they were off steroid while three patients worsened when they were still getting full dose of steroids ie 1 mg/kg/day. In case of patients with paradoxical response, either the dose of steroid was stepped up or steroids were reintroduced. In five of the 10 patients with paradoxical response, second line ATT, ciprofloxacin/ofloxacin was added. In one patient, ethionamide was also added in addition to ciprofloxacin. The addition of fluoroquinolones or ethionamide was done on empirical basis only because in none of our cases, AFB could be cultured and hence sensitivity determination was not possible. All the patients eventually recovered completely or with some residual deficit. Summary of the ten cases is given in the Table 1.

DISCUSSION

Paradoxical response is now increasingly being recognized

Table 1

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age/sex (yr)</th>
<th>Group</th>
<th>Initial therapy (months)</th>
<th>Paradoxical reaction</th>
<th>Interval to paradoxical therapy</th>
<th>Change in therapy</th>
<th>Total duration</th>
<th>Final outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>24/M</td>
<td>A</td>
<td>RHEZ + Steroid</td>
<td>Appearance of tuberculoma</td>
<td>17 months</td>
<td>↑ Steroid and ATT + ciproflox</td>
<td>34</td>
<td>Recovered with residual optic atrophy</td>
</tr>
<tr>
<td>2.</td>
<td>16/M</td>
<td>A</td>
<td>RHEZ + Steroid</td>
<td>Appearance of tuberculoma/infarct</td>
<td>6 weeks</td>
<td>Ciproflox added</td>
<td>24</td>
<td>Recovered with partial residual hemiparesis</td>
</tr>
<tr>
<td>3.</td>
<td>16/F</td>
<td>A</td>
<td>RHEZ + Ethionamide + Steroid</td>
<td>Appearance of REL /infarcts</td>
<td>4 weeks</td>
<td>↑ Steroid</td>
<td>16</td>
<td>Recovered with residual hemiparesis</td>
</tr>
<tr>
<td>4.</td>
<td>16/F</td>
<td>A</td>
<td>RHEZ + SM + Steroid</td>
<td>Appearance of fresh tuberculoma and ↑ size of pre-existing lesion</td>
<td>4 months and 2 weeks</td>
<td>Addition of ciproflox and ethionamide</td>
<td>30</td>
<td>Residual B/L optic atrophy and left hemiparesis</td>
</tr>
<tr>
<td>5.</td>
<td>13/F</td>
<td>B</td>
<td>RHEZ + Steroid</td>
<td>↑ size and appearance of new tuberculoma</td>
<td>5 months</td>
<td>No change</td>
<td>24</td>
<td>Recovered</td>
</tr>
<tr>
<td>6.</td>
<td>20/F</td>
<td>B</td>
<td>RHEZ + Steroid</td>
<td>Appearance of new tuberculoma</td>
<td>8 months</td>
<td>Addition of ofloxacin and ↑ steroid</td>
<td>18</td>
<td>Recovered with B/L optic atrophy and mild residual paraparesis</td>
</tr>
<tr>
<td>7.</td>
<td>18/F</td>
<td>C</td>
<td>RHEZ + Steroid</td>
<td>Appearance of fresh tuberculoma on therapy</td>
<td>16 months</td>
<td>Contd. ATT</td>
<td>30</td>
<td>Recovered</td>
</tr>
<tr>
<td>8.</td>
<td>28/F</td>
<td>A</td>
<td>RHEZ</td>
<td>Appearance of new tuberculoma</td>
<td>6 weeks</td>
<td>Steroid started</td>
<td>16</td>
<td>Recovered</td>
</tr>
<tr>
<td>9.</td>
<td>15/F</td>
<td>C</td>
<td>RHEZ + Sparfloxacin + Steroid</td>
<td>Reappearance / expansion of tuberculoma</td>
<td>4 months</td>
<td>Steroid restarted</td>
<td>30</td>
<td>Recovered with mild residual hemiparesis</td>
</tr>
<tr>
<td>10.</td>
<td>22/M</td>
<td>D</td>
<td>RHEZ</td>
<td>Appearance of intracranial tuberculoma</td>
<td>3 months</td>
<td>Ciproflox</td>
<td>30</td>
<td>Recovered</td>
</tr>
</tbody>
</table>
as a cause of subsequent deterioration in cases of CNS tuberculosis despite adequate and appropriate therapy. This phenomenon complicates the decision about the therapy of CNS tuberculosis. It is not possible to clearly differentiate between paradoxical deterioration and development of secondary resistance in the absence of positive tests of culture and sensitivity for Mycobacterium tuberculosis. CSF culture is positive for M. tuberculosis in less than 50% of clinically diagnosed cases of TB with an average of approximately 50%. In cases of tuberculomas, CSF findings are unremarkable or show a mild nonspecific increased protein content and bacteriology is mostly negative. In most of Indian reports, culture positivity for the Mycobacterium is relatively rare. In such a situation, a lot depends on clinical judgement and close follow-up of the patients. In none of our cases, positive culture and sensitivity reports were obtained. However, all of our patients recovered with no or minimal alteration of therapy as indicated earlier. Over the last decade, there have been scattered case reports of paradoxical response in patients with extracranial and intracranial tuberculosis particularly development of intracranial tuberculoma or clinical deterioration of previously responding patient on antitubercular therapy. Paauranic et al reported two patients of TBM who developed tuberculoma during the course of regular chemotherapy and reviewed 12 similar cases collected from literature. Malik et al described a case of paradoxical expansion of cerebral tuberculoma during therapy for Pott’s spine. SK Ajay et al reported a case of development of intracranial tuberculoma during treatment for miliary tuberculosis, which was otherwise responding to ATT. Our series of 10 patients with paradoxical response is one of the large series being reported from India. Our patients comprised of all the practical situations like tuberculoma developing in patients with TB meningitis (Group A and B), appearance of new tuberculomas and/or expansion of pre-existing tuberculoma (Group C) and development of intracranial tuberculoma in patients with initial extracranial manifestations of tuberculosis only (Group D). Paradoxical response has been reported as early as two weeks and as late as 18 months after the initiation of ATT by various authors. In our cases, the interval between the institution of therapy and appearance of paradoxical response was four weeks to 17 months, which is similar to that reported in various case reports and short series in the world literature. Bentoosh Afghani and Jay M Lieberman in their review of world literature from 1969 to 1994 found 23 cases of paradoxical enlargement of tuberculoma and 17 cases of appearance of tuberculoma while on ATT for extracranial and/or intracranial tuberculosis. They observed that interval to appearance of tuberculoma, ranged from four weeks to nine months and time to enlargement ranged from two weeks to 27 months. There is bound to be anxiety while treating such cases when patient’s condition starts worsening after initial improvement or new lesions appear on imaging of the patients. In one of our patients, only radiological deterioration was noted while patient was improving clinically. Even the patient and her parents understandably became apprehensive. We closely followed up the patient and the patient recovered without any major change in regimen except for introduction of ofloxacin. The solution to this dilemma of paradoxical response with negative laboratory support, lies in close monitoring of patient with continuation of drugs already in use with addition of steroid, increasing the dose of drugs already in use and/or addition of second line ATT.

The explanation for paradoxical response to treatment remains unclear. Various hypotheses have been put forward to explain this unusual phenomenon. One possibility is that this occurs because of decreased penetration of antitubercular drugs into brain. Restoration of blood brain barrier with appropriate treatment is proposed to result in reactivation of latent foci. However, this hypothesis cannot explain the development or enlargement of intracranial tuberculosis who are treated with isoniazid and pyrazinamide, both of which freely cross the blood brain barrier in the absence of inflamed meninges. This does not explain the improvement observed in patients in whom significant change is made in antitubercular therapy. Enlargement of lymph nodes (which do not have the barrier like blood brain barrier) in patients on anti-tubercular therapy further goes against the hypothesis. The most likely explanation for paradoxical response is interplay between host’s immune response and the direct effect of mycobacterial products. It is well known that active tuberculosis leads to depression of delayed type of hypersensitivity response due to activation of monocytes by protein derivatives of mycobacteria. Increased interleukin levels resulting from this can lead to immunosuppression. Specific antigens such as D-Arabino-D-galactonic acid bacilli lead to production of immunosuppressive concentration of prostaglandin-E2. Once active tuberculosis is under control and immunosuppression resolved, enhanced delayed type hypersensitivity and, activation and accumulation of lymphocytes and macrophages at the site of bacterial deposition or toxin production occurs when bacilli die. The reason for occurrence of this response in only some cases and not all suggests that it depends on host immune responses, virulence of tubercle bacilli, antigen load and effective antitubercular therapy.

In view of the AIDS and MDR tuberculosis, it is essential that particular attention be paid to isolation of M. tuberculosis and determination of it’s sensitivity at the outset. The review of literature suggests that centrifuging the CSF, preparing thick smears from cobweb and increasing the examination time can increase the yield of AFB culture from CSF. Repeated lumbar puncture and CSF examination can increase the yield to 87%. However, CSF smear positive for tubercle bacilli may not necessarily be positive on culture. Nevertheless, even CSF examination cannot solve the problem of isolation of mycobacteria in cases of intracranial tuberculomas. Biopsy of the lesion may be only, but not necessarily, feasible, option in such situations. In the final analysis, clinical judgement, regular follow up, guarded reassurance of patient and recognition of the possibility of paradoxical response is the only practical answer.
REFERENCES


Announcement

NAPCON 2003 - National Conference of Pulmonary Diseases - Fifth Joint Conference of Indian Chest Society and National College of Chest Physicians, India will be held at Coimbatore from November 12 to 16, 2003.

The joint partners of this conference will be ACCP, ATS, ERS, INSERM, ACCCM and AASM.

For further details please contact: Dr. T Mohan Kumar, Organising Secretary, NAPCON 2003, 12, Cowley Brown Road, RS Puram, Coimbatore 641 002, Tamil Nadu, India.

Phone No. 91422 2553890/2541484; Fax : 2553890;
E-mail : tmkdr@sify.com; tmkdr@hotmail.com, mthekkinkattil@yahoo.co.in, rpgls107@vsnl.com

Sd/-
TM Kumar