

# Duration of anti-tuberculous therapy in children with persistent tuberculomas

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## Abstract

The usual treatment duration of tuberculomas recommended is 1 year. While anti-tuberculous therapy is of absolute necessity for the treatment of central nervous system tuberculosis, no clear guidelines exist regarding the duration of therapy in case of persistent tuberculomas. We present a series of six cases of children with central nervous system tuberculosis who received anti-tuberculous therapy for a period varying between 23 and 32 months depending on the resolution of lesion seen in neuroradiological scans of the patients. Decrease in number and size of granuloma were noted in all patients while one patient showed complete resolution. After stopping anti-tuberculous therapy, the size of the granuloma remained the same, while in one patient an increase was noted. Thus, the duration of anti-tuberculous therapy in patients with tuberculoma may vary and may be required for longer time based on treatment response.

## Keywords

Anti-tuberculous therapy, tuberculoma, tubercular meningitis, children

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## Introduction

Tuberculosis (TB) of the central nervous system (CNS) is a rare complication of pulmonary TB occurring in only 1% of TB patients.<sup>1,2</sup> Hematogenous spread of mycobacterium tuberculosis (MTB) from primary pulmonary infection leads to CNS infection in the form of small discrete foci in the brain and spinal cord. These foci might either rupture into the subarachnoid space to cause tubercular meningitis or enlarge without rupturing to form a tuberculoma.<sup>3</sup> Anti-tuberculous therapy (ATT) must be administered to the patient as soon as tuberculoma is suspected, but there is no consensus regarding the duration of ATT.<sup>4</sup> The British infectious society suggests that ATT for CNS TB should comprise isoniazid (H), rifampicin (R) for a minimum of 12 months supplemented with pyrazinamide (Z), ethambutol (E) for the initial 2 months administered daily.<sup>5</sup> The Revised National Tuberculosis Control Programme (RNTCP) recommendation for CNS TB is ATT comprising of HRZE taken daily during the intensive phase for 2 months, which can be extended by a month if the child shows poor response at the end of 8 weeks, and a continuation phase consisting of HRE10 of daily months taken, which can be extended by 3 months depending on the case at the discretion of the physician. However, the ideal duration of ATT in patients with persistent tuberculomas is not known. We present a case series of patients with tuberculomas who required ATT (with daily therapy) for a variable duration of time.

## Case report

### Case 1

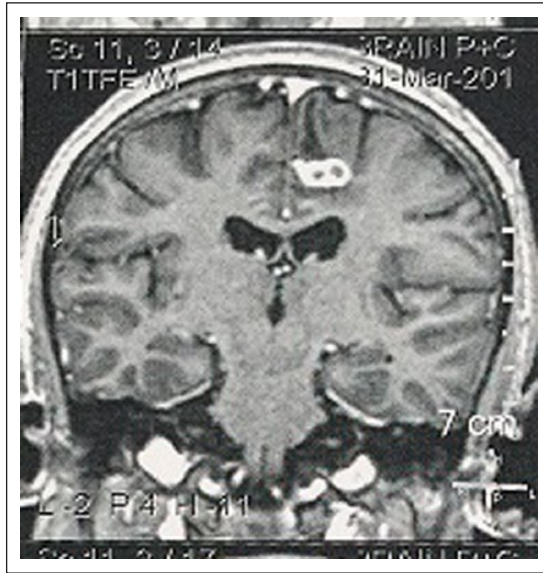
An 18-year-old girl with type 1 diabetes mellitus presented with focal convulsions in September 2012. She was detected to have multiple tuberculomas. Biopsy of one of the lesion grew MTB. She was on second-line ATT since September 2012 as drug-sensitivity testing (DST) of the tuberculous lesion showed resistance to isoniazid (INH), rifampicin (R), pyrazinamide (Z), ethambutol (E), moxifloxacin (Mfx), ofloxacin (Ofx) and ethionamide (Eth). Her cerebrospinal fluid (CSF) examination was normal. She was put on capreomycin, PAS, cycloserine (Cys), clofazimine and linezolid (Lnz) along with carbamazepine and levetiracetam and prednisolone (1 mg/kg/day for 30 days and then tapered off in next 1 month). In February 2013, she had moderate sensorineural hearing loss, and capreomycin was omitted. Her serial magnetic resonance imaging (MRI) brain till August 2013 showed decrease in size and number of the granulomas in the frontal periventricular

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**Figure 1.** MRI brain showing granulomas in the frontal parenchyma.

parenchyma bilaterally, but the left frontoparietal granuloma remained the same. In February 2014, Lnz and Cys were stopped and clarithromycin was added due to tingling and numbness in the right leg. In February 2015, computed tomography (CT) brain still showed presence of left frontal granuloma. In May 2015, her ATT was stopped, as she had completed 2 years 6 months of therapy and was asymptomatic except for persistence of left frontal granuloma. In April 2016 (Figure 1), granulomas remained the same in the frontal parenchyma, while the rest of the lesions had calcified, but the patient remained asymptomatic.

### Case 2

A 10-years-old boy was diagnosed with tuberculous meningitis (TBM) and started on ATT consisting of HRZS along with prednisolone (2 mg/kg/day) in September 2012. CT brain showed calcific densities in the parietal lobe of the cerebrum. Cerebrospinal fluid (CSF) examination showed proteins of 248 mg/dL, sugar of 36.8 mg/dL, 100 white blood cells (WBCs) with 91% lymphocytes and 10 red blood cells (RBCs) per high-power field (hpf). In October 2012, he still had persistent fever. CT brain in October 2012 showed multiple tuberculomas with persistent meningeal enhancement, following which Eth and Ofx were included in the ATT, and steroids were gradually tapered. Streptomycin was discontinued after completion of 2 months of ATT. Serial MRI brain showed regression in size of granulomas. In January 2014, the patient was asymptomatic, and his MRI brain showed decrease in size and number of granulomas. His Eth and Ofx were discontinued. His ATT was stopped in March 2015. MRI still showed presence of granulomas though with reduction in size. He is subsequently lost to follow-up.

### Case 3

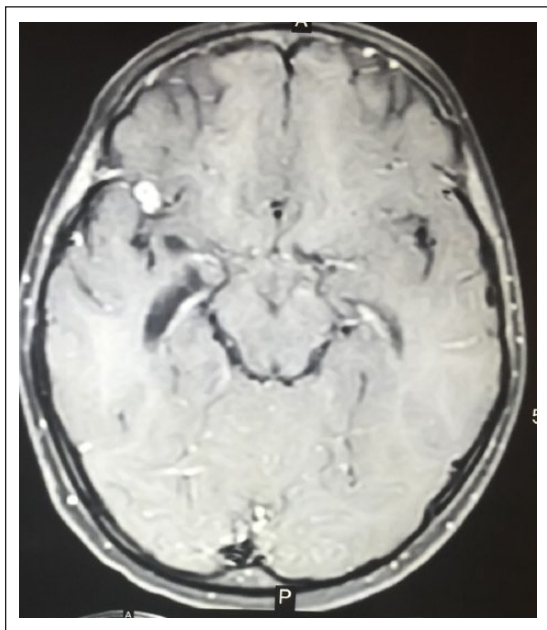
A seven-and-a-half-year-old boy had focal convulsions in February 2012. He was diagnosed to have tuberculomas on CT brain, and CSF examination was normal and was started on four drug ATT (HRZE) in February 2012 along with prednisolone (2 mg/kg/day for a month and then tapered off in next 1 month) but had no response and had increase in size of granulomas even after 1 year of ATT. In February 2013, histopathological examination done on an excised lesion removed by right parietal craniotomy which showed large granulomatous lesions with central caseous necrosis. Acid-fast bacilli (AFB) was not seen, and TB culture was also negative. He was started on second-line drugs consisting of Mfx, Eth, PAS, Cys, Lnz, amikacin (Am) and clofazimine along with prednisolone (2 mg/kg/day for a month and then tapered off in the next 3 months). In August 2013, Am was discontinued. By August 2014, MRI brain showed calcified granulomas (left occipital 36 × 19 mm and right parietal 24 × 19 mm). ATT was stopped in August 2014. On last follow-up in October 2016, he continues to remain asymptomatic, and granulomas have regressed further but still are persistent.

### Case 4

A four-and-a-half-year-old boy presented with progressive left-sided facial palsy and hemiparesis with spasticity in July 2012. He had previously been treated for multiple tuberculomas from June 2010 till January 2012 with first-line ATT. At that time, he had focal convulsions with facial palsy. CSF examination has shown 10 cells/hpf, (8 lymphocytes) and 159 mg/dL proteins. MRI brain in July 2012 showed multiple tuberculomas. He was restarted on ATT (HRSEZ) along with prednisolone (2 mg/kg/day for a month and then tapered off and kept on a minimal dose of 2.5 mg/day till April 2013). Streptomycin was stopped after 2 months. In October 2012, MRI brain showed similar picture as that of July 2012. Drug-resistant TB was suspected. Hence, second-line drugs which included Am, Mfx, Eth, PAS and Cys were started. In April 2013, MRI brain showed decrease in the number and size of the lesions. Am was stopped after 6 months of therapy. Cys was subsequently stopped in June 2013 in view of hyperactivity and hyperintensity in the dentate nucleus (Figure 2). In February 2015, most of the granulomas had regressed though right sylvian fissure nodule (0.5 × 1.0 cm) increased in size. ATT was stopped in February 2015. In August 2016, MRI brain continues to remain the same, but the child is asymptomatic.

### Case 5

A 4-year-old boy presented with limping of the right lower limb in October 2011. He was already on three drugs ATT (HRZ) for the past 6 months in view of TBM (details of which are not available, as he was treated at another centre). On examination, he had right lower limb spasticity with brisk reflexes. CSF showed proteins of 130 gm/dL, WBC



**Figure 2.** MRI brain showing tuberculoma and hyperactivity and hyperintensity in the dentate nucleus.

count of 12 cells/cumm (100% lymphocytes) and sugar of 76 mg/dL and CSF culture for TB was sent. MRI brain and spine showed tubercular granuloma in the mesial cortex of the right temporal lobe and dorsal spinal cord with associated meningitis and hydromelia. He was started category 2 ATT comprising of HRSEZ along with prednisolone (2 mg/kg/day). TB culture did not grow any organism after 6 weeks. In December 2011, streptomycin was stopped after 2 months. In January 2012, EZ were omitted, and steroids were stopped in February 2012. After serial MRIs showing decrease in size of granulomas, MRI brain and spine in March 2013 showed resolved granulomas. ATT was stopped subsequently.

### Case 6

An 8-year-old girl was referred in January 2012 for further management of her TB. In March 2011, she had convulsions and vomiting. CT brain revealed multiple tuberculomas, and Mantoux test was positive. She was started on HRSE. CSF examination was not done. In October 2011, CT brain showed increase in size of granulomas with appearance of new granulomas, and she developed drug-induced hepatitis. Her ATT was changed to Ofx and E. She was restarted on HR in December 2011 in addition to E and Ofx. On presentation to us in January 2012, she was symptomatic and ATT was shifted to HR. In April 2012, her MRI brain showed that the lesions in the left medial temporal, right temporal and right parietal lobe had resolved but the lesion in the left opercular cortex was unchanged in size and morphology. In May 2012,

she was advised to discontinue HR and was started on E and Ofx in view of increase in serum glutamic pyruvic transaminase (SGPT) levels. By July 2012, she was shifted back to HR and E, and Ofx was stopped. In March 2013, her ATT was stopped after 2 years of ATT. She continued to remain asymptomatic. In May 2013, MRI brain showed decrease in size of the left opercular lesion.

### Discussion

Duration of ATT in patients with persistent tuberculomas remains unknown. During the treatment of CNS TB, enlargement of pre-existing tuberculomas or appearance of new tuberculomas have been reported. Paradoxical enlargement of lesion is usually seen between 4 weeks and 17 months of instituting ATT. While the exact pathogenesis is not known, an immunological mechanism is suspected. The interaction between mycobacterial toxins and host immunity results in the enlargement. In such cases, the same ATT must be continued, and steroids must be supplemented or increased.<sup>6-8</sup> Gupta et al.<sup>7</sup> showed that a period ranging from 16 to 34 months of ATT is required in such patients. Afghani and Lieberman<sup>8</sup> reported that ATT for 12–18 months of ATT is required for the recovery of such patients. A study by Ahmet et al. involving 214 children between the age of 3 months and 15 years suffering from varying grades of CNS TB showed that patients with tuberculomas responded to ATT, comprising HR along with Z or S for 2 months followed by HR for 10 months supplemented with steroids for a period of 3–4 weeks though therapy was extended to 2 years for two patients for achieving complete regression of the lesions. Even after receiving ATT, 23% of the patients died.<sup>9</sup> Poonnoose et al. conducted a study consisting of 28 patients of ages between 5 and 48 years who received ATT, comprising HR for a period of 18 months. Complete resolution at the end of 9 months was seen only in 18.2% of patients while 54% of patients showed complete resolution at the end of 24 months of ATT. Around 69.2% of patients had residual tuberculomas at the end of 18 months. The rate of resolution of tuberculomas was independent of the number of tuberculomas, corticosteroid supplementation, prior ATT or duration of symptoms before presentation but was inversely proportional to the size of the lesion.<sup>10</sup> The relationship between the duration of ATT and size of the tuberculoma was established by Gupta et al. The response of 44 tuberculomas in 31 patients to ATT was recorded by MRI. It was noted that 39 tuberculomas under the size of 2.5 cm completely resolved within 5–8 months of ATT, while of the remaining five tuberculomas greater than 2.5 cm in size, four tuberculomas reduced to half their size with a year of ATT and one was completely excised.<sup>11</sup> Although the RNTCP recommendation for CNS TB is a 12 months, we chose to give longer duration in our patients due to persistence of granulomas.

Similarly, in our patients, the rate of decrease in size of tuberculoma was inversely proportional to the size of the lesion. Whether this would translate into longer treatment duration is unknown as we saw in our patients where even after stopping ATT, some of them had persistent granulomas but continued to remain asymptomatic. While complete resolution of lesion was seen in only case 5 after completing 23 months of ATT, all other cases except case 4 showed persistent granulomas though a decrease in size and number of granulomas noted after receiving ATT for a period of 24–32 months. The patients remained asymptomatic after stopping ATT but the size of the persistent granulomas remained the same except in case 4 where an increase in the size of the sylvian fissure nodule was seen. It is also necessary to change the drugs depending on patient compliance as was seen in case 4, in which the Cys was discontinued as hyperactivity, and hyperintensity was seen in the dentate nucleus and case 6 where HR were temporarily discontinued as the patient developed hepatitis. DST also plays a vital role in treatment as seen in case 1, where DST showed resistance to HRZE, Mfx, ofx and Eth and Case 4 where the patient did not respond to first-line drugs. In such cases, susceptible second-line drugs are to be used. The variable response time can also be attributed to the difference in the regimens of the 6 cases. Patients on first-line therapy including HR have shorter treatment duration than patients on second-line therapy. The choice of fluoroquinolone also affects the duration of treatment as Mfx is known to have better CSF penetration as compared to Ofx which was used in some cases.<sup>12,13</sup> Therefore, for the treatment of CNS TB, the drug selection should depend on susceptibility studies and patient compliance while the duration of treatment cannot be standardized. ATT must be guided by neuroradiological studies and clinical response.

## Conclusion

No clear guidelines exist regarding to the duration of therapy in case of persistent tuberculomas. Based on our case series, we find that duration of ATT in patients with tuberculoma may vary and ATT may be required for longer time based on treatment response.

## Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

## Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

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## Informed consent

Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

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