

# Chronic Granulomatous Disease Presenting With *Salmonella* Brain Abscesses

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**Abstract:** Chronic granulomatous disease is a rare primary immunodeficiency caused by phagocytic cell defect. We describe the case of 43-month-old boy with chronic granulomatous disease presenting with *Salmonella* spp brain abscesses, together with a review of the 13 cases reported in the literature.

**Key Words:** chronic granulomatous disease, brain abscess, *Salmonella* spp, treatment, review of literature

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Chronic granulomatous disease (CGD) is an inherited immunodeficiency disorder which results from the absence or malfunction of nicotinamide adenine dinucleotide phosphate oxidase subunits in phagocytic cells. CGD patients are susceptible to recurrent life-threatening bacterial or fungal infections as well as granuloma formations. Brain abscesses are rarely reported in patients with CGD, accounting for <5% of all infections.<sup>1</sup> We describe the case of a child with multiple brain abscesses as the initial presentation of X-linked CGD and review the corresponding literature.

## CASE REPORT

This boy is the only child of a non-consanguineous couple. The neonatal history was normal and he had received all the recommended immunizations. At the age of 36 months, he was hospitalized for an enteritis. Vidal-Wright tests resulted positive for *Salmonella typhi* AgO. The patient was initially treated with ceftriaxone. In view of the persistence of clinical symptoms and positive stool cultures for multiresistant *Salmonella Typhimurium* variant Copenhagen, treatment with imipenem was given for 3 weeks resulting in complete remission. Despite appropriate clinical and laboratory follow up, he suffered from 2 further episodes of enteritis of unknown etiology.

In January 2013, at the age of 43 months, he was admitted to our Unit with a history of 7 days of fever and headache associated with ataxia, mild ptosis of the right eye and left angle mouth deviation. A complete blood count revealed normal white blood cells

count (10,030/ $\mu$ L) and mild thrombocytosis (589,000/ $\mu$ L). Inflammatory markers such as erythrocyte sedimentation rate (16 mm/h) and C reactive protein (1.32 mg/dL) were slightly elevated. A blood culture obtained on admission, resulted positive for *Salmonella* spp. computed tomography and magnetic resonance imaging (MRI) of the brain showed multiple ring enhancing lesions in the cerebrum consistent with brain abscesses: a major formation on basal ganglia and 2 minor formations in the left cortical frontal and right temporal regions (as shown in Figure, Supplemental Digital Content 1, <http://links.lww.com/INF/B829>). He was initially treated for 7 days with intravenous meropenem and ceftazidime, according to antibiotic susceptibilities.

Cerebrospinal fluid appeared macroscopically clear, with normal concentrations of protein and glucose. Direct bacterioscopic examinations with Gram stain as well as periodic acid-Schiff and Ziehl-Neelsen stains were negative. Galattomannan also resulted negative. Cerebrospinal fluid cultures resulted sterile. Cytologic examination did not reveal any neoplastic cells.

On the basis of the history of recurrent and resistant Salmonellosis, a complete immunologic evaluation was performed. Nitroblue tetrazolium test and dihydrorhodamine 1,2,3 Assay demonstrated that the patient's stimulated neutrophils failed to generate reactive oxygen products, leading to the diagnosis of CGD. A definitive diagnosis of X-linked CGD was based on the detection of a nonsense mutation (c.469C>T, p.R157X) in the gene encoding the gp91<sup>phox</sup> (*CYBB*). Genetic testing in the family identified the mother as carrier of the mutation.

Based on the diagnosis of X-linked CGD, intravenous voriconazole (VCZ) was added to the therapy for possible mould co-infection and ceftazidime was replaced by ciprofloxacin. A complete resolution of the clinical picture was obtained. This treatment was continued for 8 weeks, until discharge. Ten months after discharge, MRI scanning showed significant reduction in the size of the brain lesions with no evidence of active disease (as shown in Figure, Supplemental Digital Content 2, <http://links.lww.com/INF/B830>). He is currently in good clinical condition, receiving standard prophylactic treatment and awaiting an unrelated bone marrow transplantation from a suitably matched donor.

## DISCUSSION AND LITERATURE REVIEW

CGD is a rare primary immunodeficiency, occurring in about 1 in 250,000 live births. CGD results from the absence or malfunction of nicotinamide adenine dinucleotide phosphate oxidase subunits in phagocytic cells.<sup>2</sup> In 65% of all cases, the defect is a consequence of mutation of the *CYBB* gene (Xp21.1); the remaining 35% are inherited in an autosomal recessive manner.<sup>3</sup> Because of a defective innate immune system, the patients suffer not only from serious infections, but also from exuberant inflammatory responses leading to granuloma formation. Life-threatening infections usually become apparent in the first years of life and are typically caused by intracellular catalase-positive microorganisms. The most common infections encountered in CGD are: pneumonia, cutaneous abscess, lymphadenitis, hepatic abscess, osteomyelitis

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**TABLE 1.** Clinical-therapeutic Findings in CGD Patients With Brain Abscesses

|                         | Dean et al <sup>5</sup>  | Agus et al <sup>6</sup>   | Nagatomo et al <sup>7</sup>                | Saulsbury <sup>8</sup>                         | Ma et al <sup>9</sup>                       | Alsultan et al <sup>10</sup>                            | Bath et al <sup>11</sup>                               |
|-------------------------|--|---|--|--|---|---|--|
| Age at diagnosis of CGD | 8 mo   | 6 mo  | 7 yr                                       | 6 mo   | *   | 8 yr  | *  |
| Inheritance             | AR   | *   | XL   | XL   | XL  | XL  | *  |
| Prophylaxis             | *  | *   | *  | TMP-SMX  | *   | Not done previously                                     | TMP-SMX, VCZ and IFN $\gamma$                          |
| CNS involvement         |  |   |  |  |   |   |  |
| Age                     | 2 yr   | 5 ½ yr  | 20 yr                                      | 11 yr  | 44 mo                                       | 8 yr  | 23 yr  |
| Clinical presentation   | Focal unilateral seizures  | Vomiting and severe headache  | Headache, fever                            | Headache, fever                                | Seizures, fever, macupapular rash           | Headache, double vision, papilledema and VI nerve palsy | Grand-male seizures                                    |
| Pathogen                | <i>Aspergillus</i>   | <i>Candida</i>  | <i>Streptococcus intermedius</i>           | <i>A. fumigatus</i>                            | <i>S. enterica</i>                          | <i>A. fumigatus</i>                                     | <i>Scedosporium prolificans</i>                        |
| Localization            | Solitary lesion (posterior frontal convexity of left hemisphere) | Solitary lesion (region of cistern magna, lateral ventricles, cerebellum) | Solitary lesion (left parietal hemisphere) | Solitary lesion (right lobe of the cerebellum) | Multiple lesions (right tempoparietal area) | Multiple cerebrum and cerebellum lesions                | Solitary lesion (right fronto-temporal area)           |
| Therapy                 | Surgical excision  | AmB, steroids   | Carbapenem and Neutrophils transfusion     | Surgical drainage, ICZ, AmB and IFN $\gamma$   | Ceftriaxone, ceftazidime and IFN $\gamma$   | Drainage, L-Am B, VCZ and IFN $\gamma$                  | VCZ, Neutrophils, transfusions, IFN $\gamma$ and GCS-F |
| Outcome                 | *  | Complete resolution   | Improvement                                | Complete resolution                            | Improvement                                 | Improvement   | Complete resolution                                    |

\*Unknown.

AR, autosomal recessive; XL, X-linked; TMP-SMX, trimethoprim-sulfamethoxazole; CNS, central nervous system; ICZ, itraconazole; AmB, amphotericin B; L-Am B, liposomal amphotericin B; BMT, bone marrow transplantation.

and perirectal abscesses. Brain abscesses are reported very rarely in patients with CGD, accounting for <5% of all infections.<sup>1</sup>

The most frequent microorganisms cultured from brain abscesses are *Aspergillus spp*, *Salmonella spp*, *Klebsiella spp* and *Staphylococcus aureus*.<sup>4</sup> A summary of clinical aspects of reported patients with brain abscess in CGD is shown in Table 1. In most of the cases, the etiology was represented by fungal pathogens, in particular *Aspergillus spp*. The number and localization of abscesses are quite variable: about half of the patients presented a single cerebral localization, whereas the other half had multiple lesions within the brain. The frontal lobe is often involved in the case of solitary lesions. One child had extensive spinal cord infection as the primary neurologic manifestation.

Diagnosis of CGD was made at a mean age of 55 months (median 43 months, range 6–192 months). The commonest symptoms at presentation were seizures, headache and vomiting. Fever is not a common symptom and has been reported in only 4 patients, combined with elevation of inflammatory markers. An asymptomatic presentation is extremely uncommon as reported in the single case described by Schutz et al.<sup>12</sup> Patients with known bacterial infections frequently showed an acute onset with fever and elevation of inflammatory markers, whereas in the case of fungal infections, most patients showed a subacute onset.

MRI is the most sensitive and specific diagnostic test for brain abscesses. Diffusion-weighted MRI and magnetic resonance

spectroscopy can be helpful in cases where it is difficult to differentiate between a brain abscess and a tumor and potentially to differentiate between fungal and bacterial causes.<sup>18</sup>

Clinical management of the reported patients has been heterogeneous. There has been only 1 report of traditional open craniotomy with complete excision of the mass, which was performed in the earliest case described in 1993 by Dean et al.<sup>5</sup> Many patients recovered with antimicrobial therapy, sometimes combined with a minimally invasive approach such as surgical drainage. A surgical approach is used less frequently because of the significant morbidity associated with immunodeficiency and with the invasiveness of the procedure and also because of the great therapeutic success obtained with antimicrobial therapy alone. Improvement or complete resolution with no neurologic sequelae has been obtained in 6 patients with antimicrobial therapy alone. However, surgery is often necessary to obtain biopsy for an accurate diagnosis and there are some suggestions that an aggressive surgical approach improves prognosis in central nervous system aspergillosis.<sup>14</sup>

Management of pediatric brain abscesses is extremely variable. The choice, duration and administration route of empiric antibiotics were not clearly defined, illustrating a lack of consensus guidelines. Ceftriaxone/cefotaxime plus metronidazole has been recently recommended for use in immunocompetent children, whereas meropenem has been proposed as a good first-line choice for immunocompromised patients, in whom outcome is poorer.<sup>19</sup>

| Schuetz et al <sup>12</sup>     | Hipolito et al <sup>13</sup>  | Metin et al <sup>14</sup>                           | Bukhari and Alrabiaah <sup>15</sup>              | Patiroglu et al <sup>16</sup>                  | McNeil et al <sup>17</sup>   | Our patient  |
|---------------------------------|---|---|--|--|--|--|
| 18 mo                           | *   | 4 yr  | *  | 16 yr  | *  | 43 mo  |
| XL-McLeod phenotype             | *   | XL  | *  | AR   | *  | XL   |
| TMP-SMX, ICZ                    | TMP-SMX, ICZ  | Not done previously                                 | *  | Not done previously                            | TMP-SMX, itraconazole (noncompliance)  | Not done previously  |
| 6 yr<br>Incidental diagnosis    | 5 yr<br>Focal seizures on right arm, sinusitis, lymphadenopathy               | 4 yr<br>Headache, vomiting, backache, paraplegia    | 5 yr<br>Torticollis, upper back swelling         | 16 yr<br>Seizures                              | 24 yr<br>Tonic clonic seizure, right-sided facial droop, left arm weakness       | 43 mo<br>Fever, mild ptosis on right eye, left angle mouth deviation, fever and ataxia |
| Suspected inflammatory etiology | <i>Alternaria infectoria</i>  | <i>A. fumigatus</i>                                 | <i>A. nidulans</i>                               | <i>A. fumigatus</i>                            | <i>Phaeoacremonium parasiticum</i>   | <i>Salmonella</i> Spp  |
| Multiple intracerebral lesions  | Solitary lesion (left parietal dorsally frontal cortex)                       | Multiple lesions (right cerebellar lobe and vermis) | Paravertebral, epidural and subcutaneous abscess | Solitary lesion (right frontal lobe)           | Multiple lesions (right temporal lobe and putamen)                               | Multiple lesions (basal ganglia and cortical frontal and temporal areas)               |
| BMT                             | L-AmB, IFN $\gamma$ , meropenem, vancomycin, ceftazidime, VCZ and caspofungin | Surgical drainage; TMP-SMX, L-AmB and IFN $\gamma$  | VCZ  | Surgical excision; VCZ, L-AmB and IFN $\gamma$ | Surgical biopsy; vancomycin, meropenem, caspofungin, L-AmB, VCZ and IFN $\gamma$ | VCZ, ciprofloxacin and meropenem   |
| Complete resolution             | Death   | Improvement   | Complete resolution                              | Complete resolution                            | Death  | Complete resolution  |

The appropriate duration of antimicrobial therapy is still unclear, ranging from 4 to 6 weeks of antibiotics if the abscess is drained, to at least 6–8 weeks with conservative treatment.<sup>20</sup> As infections often respond slowly in CGD patients, intravenous antibiotic treatment should be followed by prolonged oral treatment and an individually tailored approach guided by clinical improvement, normalization of inflammatory markers and resolution on imaging should be considered. In the case of *Aspergillus* infection, VCZ is currently considered the treatment of choice. In addition to systemic antifungal treatment, there has been some suggestion that neurosurgical procedures may improve the outcome in central nervous system aspergillosis.<sup>21</sup>

Granulocyte transfusions and Interferon gamma (IFN $\gamma$ ) have been used in severely ill CGD patients, especially in those with fungal infections. Their value, however, has not been investigated in a controlled study and their clinical use remains somewhat controversial. In addition, with the advent of potent new antifungal drugs, the use of granulocyte transfusions and IFN $\gamma$  is likely to decrease in the future.

Overall the clinical outcome was benign with only 2 cases of death, both caused by fungal etiology. It should be taken into account that a surgical biopsy was not performed in our patient, in view of the good clinical response to the rapid initiation of antibiotic/antifungal therapy. Collectively, the identification of *Salmonella* spp in blood culture, the past medical history with recurrent

*Salmonella* infections as well as the clinical improvement after empiric antibiotic therapy, led us to conclude that cerebral lesions were caused by *Salmonella* infection. Patients with chronic granulomatous disease characteristically present a susceptibility to *Salmonella* spp infections.<sup>2</sup>

Case reports of CGD-associated brain abscesses caused by *Salmonella* spp are extremely rare. To our knowledge, only 1 case has been reported thus far by Ma et al<sup>9</sup> in 2003. The patient was a 44-month-old boy, affected by CGD, who developed multiple parieto-temporal abscesses caused by *Salmonella enterica*, after a 4-week history of fever and maculopapular rash with skin nodules. Similarly to our patient, *Salmonella* was isolated from blood culture and not from cerebral biopsy. The patient recovered after prolonged antibiotic therapy with third generation cephalosporin plus IFN $\gamma$  injections. In our case also the resolution of brain infection was induced by a prolonged (8 weeks) antibiotic therapy with meropenem, in association with a broad-spectrum antibiotic such as ciprofloxacin. VCZ was also added for antifungal protection. To our knowledge, our patient is the second case of CGD-associated brain abscesses because of *Salmonella* spp, but is the first case where the brain infection was the harbinger of CGD. In conclusion, although brain abscesses are not frequently reported in CGD patients, our case emphasizes the importance of investigating a strong clinical suspicion of CGD in the setting of brain abscesses, especially when they occur early in life.

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