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**Case Report**

*Citrobacter freundii* infection in glutaric aciduria type 1: Adding insult to injury

Mukhopadhyay C, Dey A, Bairy I

**ABSTRACT**

Glutaric aciduria type 1 (GA1) is an inborn error of organic acid metabolism, where the brain is the principal organ affected with exposure to toxic metabolic product, 3-hydroxyglutaric acid (3-OHGA). A 2-year-old boy with GA1 and delayed developmental milestones had an acute neurological crisis leading to massive brain abscess with *Citrobacter freundii* infection, a rare cause of neonatal meningitis and often associated with brain abscess. Both 3-OHGA and *C. freundii* can damage the blood-brain barrier and can cause significant trauma which demands immediate and appropriate management. Encephalopathic manifestations of GA1 may consequently increase the risk of meningeal infection and it has not been previously documented.

**KEY WORDS:** Brain abscess, *Citrobacter freundii*, glutaric aciduria type 1

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In neonates, *Citrobacter* spp. (*C. koseri* and *C. freundii*) are more frequently associated with brain abscess in contrast to the leading agents, *Esherichia coli* K1 and Group B streptococci.[1,2] *Citrobacter freundii* possesses enough invasive capabilities to cross an apparently intact anatomical barrier to produce meningitis and abscess with high mortality.[2-4]

Glutaric aciduria type I (GA1) is an autosomal recessive disorder due to glutaryl CoA dehydrogenase deficiency in the degradation of lysine, hydroxylysine, and tryptophan.[9] Affected children (2-37 months) may present with macrocephaly, loss of head control, choreoathetosis, seizures, generalized rigidity, opisthotonos, and dystonia after an infectious illness.[9] The two other genotypically as well as phenotypically heterogenous varieties are GA2, an x-linked disorder with multiple acyl-CoA dehydrogenases deficiency and GA3, a rare peroxisomal abnormality.[7]

Despite massive excretion of glutarate (GA) in GA1, small excretion of 3-hydroxyglutaric acid (3-OHGA) in urine is significant, specific, and only diagnostic metabolite in some samples. Moreover, 3-OHGA can cause striatal necrosis in one-third of the patients with structural alterations in blood-brain barrier (BBB) cells like cytosol lucency, cytoskeleton break-down, mitochondrial swelling, and formation of the pinocytic vesicles.[8] The combination of fronto-operculo-temporal hypoplasia and communicating hydrocephalus are pathognomonic. Brain abscess, however, is not a common manifestation in children with GA1. Since this is the first documented case of *C. freundii* in a GA1 patient, any association with severity of Citrobacter infection remains to be seen.

**Case Report**

In March, 2006 a 2-year-old boy was admitted with fever, altered sensorium, and hurried breathing. He was previously admitted at 11 months of age with fever, drowsiness, and loss of head control without any history of infectious illness. Developmental milestones were not delayed so far. Although born prematurely by forceps delivery, there was no history of antenatal complication (weight at birth 3.5 kg). There was no immediate postnatal complication as well and no suggestive family history of GA1. The child was treated empirically with ceftriaxone and amikacin.

He was readmitted at the age of 22 months with fever and loss of head control. His milestones were severely delayed since he could only sit at that time. On examination, there was frontal bossing, ‘setting sun sign,’ absent tendon jerk, and hypotonicity. The head circumference was 52 cm (above 2 SD) with extra-axial fluid collection and mild cerebral atrophy. There was an episode of lower respiratory tract infection 3 months back when the child was treated with antibiotics without any microbiological investigation. Gas Chromatography and Mass Spectrometry (GC/MS) of urine organic compounds (Metabolic and Genetic Healthcare Services, MILS International India, Matsumoto Institute of Life Sciences, Japan) showed increased excretion of lactate 4.96 (control below 0.5 by MILS method), GA 5.30 µmol/mmol Cr (control: zero), and 3-OHGA 0.78
μmol/mmol Cr (control: zero), which is characteristic of GA1. He was treated with riboflavin (10 mg 4 tab TDS), carnitine (500 mg 1 tab BD), and diamox (250 mg 1 tab TDS).

Examination on March, 2006 revealed papilledema and bulged fontanella (head circumference = 52.5 cm), right-sided subdural effusion, diffuse cerebral atrophy, and a large abscess in right subcortical grey matter [Figure 1]. White Blood Cell (WBC) count was 30,400/cmm with 82% neutrophil, although blood and CSF culture was sterile. Thick brown putrid odor pus, approximately 200 and 50 mL was aspirated by burr hole method from brain abscess 2 weeks apart, both of which grew C. freundii in culture.

Diagnosis was done on recognition of relatively nonspecific physical findings and on performance of urine organic acid quantification by GS/MS. Characteristic findings on neuroimaging were also suggestive.

He had cefotaxime and ofloxacin (intravenously for 2 weeks), riboflavin, carnitine, diamox, and dietary protein restriction before being discharged with oral cefixime. During his last visit (August, 2006), there was a weight gain of 1.3 kg and no further change in head circumference. The child can walk without support and pronounce at least 10-11 words at the age of 34 months. He is still on riboflavin, carnitine, and diamox.

**Discussion**

Although C. freundii is responsible for occasional extraintestinal infections including development of a cerebral abscess complicating meningitis, this is, as far as our knowledge, the first documented case in a child with GA1 where ‘dual assault’ of C. freundii and 3-OHGA cytotoxicity might lead to massive abscess formation in the brain.

Free diffusion of 3-OHGA across the BBB into the CSF results in the swelling of endothelial cells and astrocytes which precedes neuronal damage.[11] Moreover, endothelial and giant endfoot swelling as well as platelet microthrombi narrow the lumen of capillaries and restrict tissue perfusion leading to necrosis of the surrounding tissue, which might accentuate simultaneous infection with an organism with more invasive property, like *Citrobacter* spp. Central nervous system (CNS) infection caused by *Citrobacter* spp. is severe in itself and interestingly these infections are usually in neonates and more often in premature infants. It is noteworthy, therefore, that the BBB damage in a 2-year-old child with GA1 is most likely to have contributed to the infection, leading to more extensive damage and ultimately formation of a massive abscess.

The mode of acquisition of the organism was not clear. Suggestive sources like infant formula feeding or metastatic seeding from distant extracranial sources (abdominal, urinary tract, and lung) had no correlation in this patient. [9,10] Although the downhill progression of the disease was preceded by an infectious episode, microbiological isolation of any bacterial agent could provide more suggestive evidence.

In conclusion, it is evident that CNS in GA1 becomes more susceptible to invasive *Citrobacter* spp., which can only be tackled with immediate diagnosis and appropriate management, especially of metabolic decompensation[11] to avoid permanent brain damage.

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