LETTER TO THE EDITOR

Correspondence Regarding: Alexander Disease Mutant Glial Fibrillary Acidic Protein Compromises Glutamate Transport in Astrocytes J Neuropathol Exp Neurol 2010;69:335–45

We read with interest the recent article, “Alexander disease mutant glial fibrillary acidic protein compromises glutamate transport in astrocytes,” by Tian et al (1). The authors documented impairment of glutamate transport in aberrant astrocytes bearing mutant glial fibrillary acidic protein (GFAP) that may play an important role in the pathogenesis of oligodendrocyte and neuronal degeneration in Alexander disease (AxD). This would partly explain the high seizure susceptibility of these patients (mainly in the infantile form) and its relentlessly progressive clinical course. The likely occurrence of excitotoxicity related to impairment of glutamate transport in dystrophic astrocytes and of their ability to metabolize extracellular glutamate in AxD was first suggested by French authors (2). In our opinion, this finding may have relevant therapeutic implications, particularly for this untreatable genetic disease. Indeed, recent experimental studies indicate that agents such as the β-lactam antibiotics can increase glutamate transporter subtype 1 (GLT-1) activity in astrocytes that are genetically impaired in their GLT-1 expression, thereby improving survival and ameliorating the neurologic features in animal models of various neurologic diseases including amyotrophic lateral sclerosis and ischemic stroke (3). Importantly, we have recently reported the long-term use of cycles of the β-lactam antibiotic ceftriaxone in a patient affected by an adult form of AxD with a rapidly progressive clinical course; this treatment apparently halted the progression of the disease and ameliorated some of the neurologic features (2). Notably, further recent findings of our group in an in vitro model of AxD confirmed the potential therapeutic role of ceftriaxone through additional complex biochemical mechanisms involving the elimination from astrocytes of the mutant GFAP and transcription downregulation (4).

Overall, these observations strongly indicate a potential therapeutic role of ceftriaxone in AxD and suggest novel therapeutic strategies directed at astrocytes for this and other similar neurodegenerative diseases.

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Authors’ Reply:

We thank Dr Sechi et al for their comments on our study of GLT-1 expression in AxD (1). They raise the interesting possibility that ceftriaxone could be used to treat AxD, drawing their conclusion from 3 observations. First, β-lactam antibiotics do increase glutamate transporter expression in astrocytes (2). Second, ceftriaxone treatment of astrocytoma cells transfected with mutant GFAP reduces the accumulation of mutant GFAP protein (3), although the mechanism(s) of this reduction is not clear. Bachetti et al (3) find that 1 mmol/L ceftriaxone (a concentration far above what is achievable clinically) significantly increases levels of the small heat shock proteins, αB-crystallin and hsp27, in astrocytoma cells, and has complex effects on proteasome activity and autophagy. The interpretation of these data is complicated by the fact that mutant GFAP accumulation itself inhibits proteasomal activity (4). αB-Crystallin will reverse this inhibition (4), suggesting that the ceftriaxone effect in cultured astrocytoma cells may be mediated in large part by its upregulation of αB-crystallin. αB-Crystallin, by itself, also partially restores GLT-1 expression in mouse models of AxD (5). Bachetti et al (3), however, did not determine whether ceftriaxone increases glutamate uptake or processing in their cellular model. Third, Sechi et al (6) reported beneficial effects of ceftriaxone treatment for a patient with adult-onset AxD. Some of the signs and symptoms improved, or at least their progression slowed, although results from the magnetic resonance imaging did not change. It is, of course, not clear that the apparent positive effect of ceftriaxone in this patient was due to the upregulation of GLT-1 or other elements of glutamate processing in astrocytes, due to a decrease in astrocyte GFAP levels, or due to some other effects. Interpreting changes in individual patients is especially difficult when the natural history of the disease includes uneven rates of progression.
REFERENCES


