Why Do Children With Propionic Acidemia Or Urea Cycle Disorders Rarely Show Autistic Behavior?

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Letter to Editor

Derrick MacFabe’s hypothesis that propionic acid generated by gut bacteria induces autism [1], while compelling, leaves one question largely unanswered: Why do children with inborn propionic acidemia rarely show autistic behavior? Although exacerbations of Propionic Acidemia (PA) bear “some resemblance” to autism spectrum disorders (ASD), MacFabe noted, only one case of autism associated with PA has been reported in the literature; these physicians stated: “In the consensus conference about diagnosis and management of PA hosted in Washington, D.C. in January 2011, there was no reported association among the neurological sequelae of the disease between PA and autism.”[2]

Other physicians who treat PA children also report they rarely show autistic behavior: Sabine Scholl-Bürgi: “In our PA patient group none has an ASD.”[3] Professor of Pediatrics: “I see lots of kids with PA and UCD [urea cycle disorders], but few (perhaps none) have ASD.”[4]

As the professor noted, children with Urea Cycle Disorders (UCD) also rarely show autistic behavior. Krivitzky et al.: “Children in this cohort [UCD] show other behavioral/ emotional strengths, including a minimal percentage with previous diagnoses of Autism spectrum disorders, mood disorders, and other psychiatric disorders.”[5] Groppman et al., however, concluded that patients with partial deficiencies of urea cycle enzymes and late-onset presentations may show signs of autism.[6]

Do children with propionic acidemia or urea cycle disorders have something in common that protects them from autistic disorders? Both are inborn errors of metabolism which induce high levels of blood ammonia, among other hazards. Children with urea cycle disorders lack one or more enzymes that detoxify ammonia to urea in the liver. Scholl-Bürgi and colleagues cited evidence implicating secondary inhibition of these enzymes in the hyperammonemia of PA.[7]. Filipowicz et al., however, concluded: “[Our] results suggested that defective formation of glutamate/glutamine, rather than a block in the urea cycle, is the likely mechanism associated with hyperammonemia in patients with propionic acidemia. [H]yperammonemia in propionic acidemia might be related to inability to maintain adequate levels of glutamine precursors through a dysfunctional Krebs cycle.”[8]

In tissues that produce large amounts of highly toxic ammonia (e.g. skeletal muscles) the enzyme glutamine synthetase converts ammonia to the amino acid glutamine for safe transport in plasma to the small intestine and conversion to urea by the liver. Ammonia generated by brain neurons is first detoxified by a-ketoglutarate, forming the neurotransmitter glutamate; astrocyte glutamine synthetase then combines ammonia with glutamate that astrocytes take up at synapses – forming glutamine, and neutralizing both precursors.

When plasma ammonia is high in urea cycle disorders (or hepatic encephalopathy) plasma glutamine is also high.[9] When plasma ammonia is high in PA, by contrast, plasma glutamine is normal or low (glutamine paradox) [7,8,10-13]. Al-Hassan and colleagues: “The mechanism that disrupts this correlation in propionic acidemia is unclear. Metabolic acidosis, which is not generally seen in UCD, may be a factor. It has been demonstrated that acute changes in pH have an effect on glutamine/glutamate metabolism. Acidosis enhances glutaminase in the kidneys, whereas in the liver it inhibits both glutaminase and glutamate dehydrogenase while stimulating glutamine synthesis.”[11] Tuchman and Yudkoff: “… in patients with severe PA, plasma glutamine levels correlate poorly with ammonia levels. The cause for this phenomenon is unknown, but may be that glutamine synthetase is inhibited by a putative toxin (e.g., propionyl-CoA), which accumulates in PA, or a low concentration of ATP, which is expected in PA, may affect this ATP-dependent enzyme.”[13]

Plasma glutamine is also low in children with ASD and brain glutamine/ glutamate (glx) also usually low measured by magnetic resonance spectroscopy (MRS) [14-18] despite their frequent high plasma ammonia.[19]. Ghanizadaeh: “The low level of plasma glutamine . . . is suggested as a screening test for detecting autism in children especially those with normal IQ. The decreased level has been reported before in all children with autism.”[20] Wakefield and colleagues suspected bacteria in their diseased intestines generated more ammonia than their impaired liver could clear, which reached the brain. Finding serum glutamine low in these children, and knowing liver dysfunction impairs astrocyte glutamate transporters, they proposed their brain glutamine was also low[21].

In children with propionic acidemia [7,10,22] or urea cycle disorders [9], by contrast, CSF/ brain glutamine is often high. Scholl-Bürgi and colleagues: “In contrast to plasma, cerebral glutamine concentrations in PA are often elevated even in metabolic stable situations. Accumulation of intracellular glutamine measured as Glx peak has been shown by magnetic resonance spectroscopy. Elevated CSF concentrations have been reported in PA patients during a stroke-like episode or in hyperammonaemia.”[7]

Davison and colleagues, on the other hand, found when PA was stable, brain glutamine was greater than normal in white matter, but much less than normal in the basal ganglia – subcortical gray matter structures deep within each hemisphere. “MRS studies undertaken during metabolic stability before any severe acute episodes beyond the neonatal period demonstrated decreased Glx in basal ganglia compared to the normal MRI comparator group but a trend to increase in white matter. Glutamine alone was significantly decreased in basal ganglia during metabolic stability.”
During exacerbations of PA, basal ganglia glx fell further: "The alterations seen in glutamate and glutamate in basal ganglia are of particular note. Glx was significantly decreased during severe acute episodes, with a smaller (non-significant) decrease noted in basal ganglia in studies acquired during metabolic stability." They concluded: "The metabolite alterations seen in propionic acidemia in the basal ganglia during acute encephalopathy reflect loss of viable neurons, and a switch to anaerobic respiration. The decrease in glutamate + glutamate supports the hypothesis that they are consumed to replenish a compromised Krebs cycle and that this is a marker of compromised aerobic respiration within brain tissue."

Horder et al. studied brain metabolites in adults with ASD by MRS at 1.5 Tesla [18]. Their thoughtful report speaks for itself: "In summary, we found preliminary evidence that adults with ASD (both narrowly and broadly defined) have significant differences in brain glutamate and/or glutamine metabolism. This may be a final 'common pathway' in the disorder, and underpin some clinical symptoms."

"Taken together, these results demonstrate that, rather than being a 'global' neurobiological abnormality, Glx changes seen in ASD are highly regionally specific, suggesting that the underlying neurobiological causes are also localized. Reductions in Glx could simply result from a local reduced density of glutamatergic synapses and neurons, such as reduced storage capacity and turnover, but could also be the product of alterations in glutamate and glutamine metabolism . . . . A further possibility is that the observed differences in Glx are secondary to alterations in other neurotransmitter systems. For example, the basal ganglia are densely innervated by serotonergic projections, which exert complex modulatory effects on glutamate and GABA release . . . ."

"We are only able to report a correlation between ASD in adults . . . and reduced basal ganglia Glx levels. Hence, we cannot be certain whether the differences in Glx are the cause of the ASD symptoms. At 1.5 T, it is not possible to distinguish between the compounds that contribute to the 'Glx' signal, that is, glutamate and glutamine. Future studies at 3 T or higher are needed to distinguish these compounds, but previous studies have cautiously attributed reductions in Glx to glutamate, as glutamate constitutes the most abundant central neurotransmitter."[18]

An MRS study of fever’s benefit in ASD might also speak for itself. The frequent ability of infectious fever to relieve autistic behavior dramatically has long tantalized parents, practitioners, and researchers. Is the decisive factor in this phenomenon the great amounts of glutamine that skeletal muscles release into blood as provisional fuel to compensate the loss of appetite of fever [19]?

The risky (but effective) antipsychotic drug risperidone (Risperdal), which calmed 54% of ASD children and adults (but aggravated 20%) [24] also suggests brain glutamine may be low. Risperidone is thought to suppress serotonin and dopamine activity at synapses, but also stimulates glutamate uptake by astrocytes and activity of glutamine synthetase [25].

Propionic acid interacting with ammonia may play a role in ASD. Burrus: "A reaction between ammonia and propionic acid should result in the production of beta-alanine, a chemical similar in composition to gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter which has been shown to be present in higher quantities in autistic patients" [26].

In 2012 I sent my paper on fever, ammonia, and glutamine in ASD [19] to all practitioners formerly listed on the Autism Research Institute (ARI) website. Ten practitioners replied they regularly give ASD children 250 mg to 8 g/day of oral glutamine to heal their intestines. One said 5 g/day was “fantastic” to heal intestines. Several warned of occasional hyperexcitability from glutamine; others found it rare. Only two, however, reported improved behavior. One was Franco Verzella, an Italian MD who gives ASD children 5-7 g/day of oral glutamine, after first cleansing their intestines of pathogens like bacteria and candida: “Multifactorial and multisystemic is the condition, so that the improvement has different aspects in different children. Most common: sedation, less stereotypes, better sleep, more concentration” [27]. At the ARI 'think tank' in Baltimore April 2013, I mistakenly reported that Verzella gave ASD children as much as 20-30 g/day of glutamine! He meant that amount was sometimes given to heal adult intestines. A neurologist at the think tank warned that oral glutamine has induced seizures in some ASD children. A word to the wise . . . .

In the small intestine, oral glutamine nourishes enterocytes and other rapidly replicating cells; also breaks down to glutamate and ammonia shunted to the liver, and citrulline, which the kidneys convert to arginine. Jon Pangborn, senior ARI biochemist, warned that intestinal bacteria and yeast can degrade oral glutamine and other amino acids to toxic metabolites. He recommended cleansing the gut of harmful bacteria and yeast before giving ASD children any amino acid except taurine, which helps detoxify ammonia [28].

MacFabe’s plausible hypothesis of ASD speaks for itself – but its implications are far-reaching. If propionic acid generated by gut bacteria induces autism, we might expect children with inborn propionic acidemia to show autistic behavior. Yet they rarely do. In light of their usual high brain glutamine – and frequent low brain glutamine in ASD – does high brain glutamine protect them?

**Postscript**

A preliminary version of this letter was sent to all attendees of the 2013 ARI think tank. These replies appear most telling:

John Green (MD): "I have found that children with dihydroxyphenylpropionic acid elevations in the urine very often have substantial elevation in autistic behaviors, responsive to antibiotics such as vancomycin or flagyl. The problem with this observation is that antibiotics may help these kids for other reasons, so it certainly doesn’t close the logical loop on MacFabe’s hypothesis. I think glutamine bears more looking into, and will look for opportunities to offer higher doses to some children to see how they respond. In particular, those who respond to fever may be a good group to try it with."

Liz Lipski (PhD), clinical nutritionist: "Oral glutamine has either no effect or good effect on GI symptoms. Dosage depends on the person; for inflammatory bowel disease in flare-up – up to 20 grams daily. For a child with autism, begin slowly with 1 gram [then] up to 5 grams depending on what’s going on and how big he/she is. If negative effects [e.g. constipation] are noticed, stop or decrease the dosage."

Richard Lord (PhD): "Propionic acidemia is a relatively common genetic condition, and most cases do not develop autism. I add my experience to those you cite, having consulted in numerous cases of transient propionic aciduria due to deficiencies of biotin or vitamin B12 in children with SIBO [small intestine bacterial overgrowth] that..."
produce increased amounts of microbe-derived propionate. Although some had been diagnosed as autistic, in general such cases do not tend to develop autistic-like symptoms. . . . The perturbation in brain systems associated with regressive autism is most likely impacted to some degree whenever propionic acidemia is present. However, those perturbations are probably of a nature distinctly different from propionate toxicity.”

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