Clinical ReviewState of the Art Review

Autism spectrum disorder: advances in diagnosis and evaluation

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Re: Autism spectrum disorder: advances in diagnosis and evaluation

In response to the new review by Zwaigenbaum and Penner (1) John Stone writes: “We come back in the end to the reality that when it comes to what could be driving these changes to our society the authors neither acknowledge the problem, or have any explanation of it. I fear they may be fiddling as Rome burns.”(2) In the interest of not “fiddling as Rome burns”, I here advance the following explanation, as an eminently testable hypothesis based on the following findings, some of which have only very recently been established:

1)ASD develops in a state of neuroinflammation in the brain. In 2011, Patterson (3) observed “an ongoing, hyper-responsive inflammatory-like state in many young as well as adult autism subjects.” In 2017, Lee et al (4) demonstrated, in postmortem ASD v normal brains, “a shift in microglial phenotype that may indicate impaired synaptic plasticity and a chronic vulnerability to exaggerated immune responses.” Specifically, they observed “a significant increase in primed microglia in gray matter of ASD compared to typically developing individuals.”

2)Microglia are brain macrophages, bone marrow-derived myelocytes that migrate to the brain during embryogenesis (5). Macrophages of all types are resident in a diverse array (perhaps all) organs, and they share not only a common embryonic origin but a common dual functionality:
a)The removal, by phagocytosis, of dead or superfluous cells and cell debris resulting from injury, natural cycles of growth and regression (e.g., in the breasts and uterus during the menstrual cycle), or the unfolding of developmental programs (e.g., normal brain development; 6,7) and
b)The destruction of invading bacteria or other microbes in response to infection, via secretion TNFα and a host of cascading toxins, i.e., inflammation. These two types of macrophage activity are initiated by distinct signaling pathways (6). Activation of inflammation where infection is not present only produces damage to normal tissues. This dual functionality of macrophages may be likened to the action of first responders such as the police. The police are called to the scene of an accident on the highway, and do what is necessary to clear the area of damaged vehicles and persons, to restore the normal flow of traffic. But whilst they are armed (e.g., in the US), they do not draw nor fire their weapons unless bad actors are present. The drawing and use of firearms may be likened to inflammation in the body.

3)Physiologically, the priming or activation of macrophages of all types, to produce inflammation, is naturally regulated by the amino acid glycine (8). This has now been confirmed experimentally in the brain in rats (9). The glycine receptor is a glycine-gated chloride channel which allows for chloride ion influx, thus stabilizing (by hyperpolarization) the macrophage plasma membrane, thus rendering them less susceptible to depolarization by

various stimuli (8). The depolarization of the macrophage plasma membrane initiates calcium ion influx and the cascade of inflammatory events. These days, plasma glycine levels are normally in the range of 150 – 350 μM, whereas glycine concentrations optimal for macrophage regulation are in the range of 0.5-1mM (8), well in excess of biochemical requirements for protein synthesis, etc.

4)There has been in recent years, in the industrialized world, a general dietary shift away from the consumption of whole meats, fish and poultry, toward the consumption of exclusively muscle meats. This has gone unnoticed, in my view, because of glycine's long having been considered "nonessential", the presumption being that the amino acid content of muscle meat provides an optimal mix of "essential" amino acids.

5)However, muscle meats are relatively methionine-rich and glycine-poor, whereas collagen is exceedingly glycine-rich (one third mole fraction) and methionine-poor (less than 1%). Metabolically, methionine and glycine have a reciprocal relationship. When a methionine-rich meal is absorbed (e.g., after a typical meat, fish or poultry meal) hepatic metabolism is switched from methionine salvage mode to methionine clearance mode, by the activation of glycine-N-methyltransferase, the main enzyme of the only clearance pathway for methionine. Each mole of methionine requires at least two moles of glycine to be cleared (10).

6)The general dietary shift toward exclusively muscle meat consumption and away from collagen (gelatin) consumption, has therefore resulted in a reduction in plasma glycine levels in the general population. While this may seem paradoxical because the typical modern omnivorous diet is rich in all the protein amino acids, the concomitant increase in dietary glycine consumption and decrease in plasma concentration has recently been demonstrated in the Oxford cohort of the EPIC study. Thus, Schmidt et al. (11) observed that while meat-eaters in the UK consumed 20% more glycine each day than vegans (3.12 v 2.61 g/day, respectively), their mean plasma free glycine level was 14% lower (390 v 452 μM, respectively) than that of vegans.

7)Hence, if there is a critical threshold concentration of plasma glycine that must be maintained for the overall optimal regulation of the innate immune system (i.e., macrophages body-wide, including microglia in the brain), it may be suggested that most in the general population (save for vegans and those who consume significant collagen) suffer a functional glycine deficiency.

8)Glycine infusion has now been shown to prevent microglial activation (8), just as earlier studies showed in animal models (9), and at least one human clinical trial, in which glycine supplementation reversed type 2 diabetes (12).

The foregoing may be distilled down to the following simple hypothesis: ASD (among many other conditions, including arthritis, diabetes, cardiovascular disease and cancer) is a manifestation of systemic glycine deficiency, resulting from consumption of a typical diet high in essential amino acids (ie., in muscle meats), but lacking in glycine (a main constituent of bone and connective tissue, which, in contrast to diets of previous generations, is typically discarded.) It may be easily corrected by supplementing the diet with either free glycine, or foods rich in gelatin (collagen), such as bone broths of any kind. It is really the extension of the whole foods approach to meat, fish and poultry as well as grains.

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