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Brain inflammation a key finding in autism

Brain inflammation is a consistent finding in autism, according to a study by researchers at Johns Hopkins.

Diana Vargas and colleagues examined brain tissue from 11 autistic individuals, ranging in age from 5 to 44, who had died of accidents or injuries. Comparing these samples to tissue from non-autistic controls, the researchers found marked activation of microglia and astroglia—cells that are among the "first-line responders" in the central nervous system's immune system—and an elevated number of cytokines and chemokines, which are immune system proteins involved in inflammatory processses. The researchers note, "The pattern of cellular and protein findings indicates that they are part of the 'innate' immune system in the brain, and do not appear to be caused by immune abnormalities from outside the brain."

> Their data, Vargas et al. say, "suggest that the pathological changes observed in the cerebellum in autistic patients do not occur exclusively during prenatal development but appear to involve a... chronic neuroinflammatory process" that continues even into the late stages of life.

Vargas et al. say their analyses showed that "regardless of age, history of epilepsy, developmental regression, or mental retardation, marked morphological changes consistent with chronic and sustained neuroglial inflammatory responses were present in cortical and subcortical white matter as well as in the cerebellum." The most striking increase in neuroglial activity was detected in the cerebellum, a brain region strongly implicated in autism. Consistent with prior reports, a loss of neurons in the Purkinje cell layer of the cerebellum was evident in nine of ten autistic subjects in this study.

The researchers say their findings are consistent with an active process of neurodegeneration and neuroinflammation, particularly in the cerebellum. Their data, they say, "suggest that the pathological changes

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Glutathione: a key to the autism-thimerosal connection?

Abnormal methylation and reduced amounts of the antioxidant glutathione may make autistic children highly vulnerable to the damaging effects of mercury and other toxins, according to a study by Jill James and colleagues. These findings, one public interest group says, "raise serious concerns about the studies that have allegedly proven the safety of mercury in vaccines."

> The "glutathione connection" could explain the high male-to-female ratio in autism, the link between autism and intestinal disorders, and the elevated incidence of autoimmune disorders in autism—as well as explaining why thimerosal could cause autism in a subgroup of exposed children.

James and colleagues compared 20 autistic children to 33 non-disabled controls and found evidence in the autistic group of impairments in methylation, a process that regulates development and cell functioning by silencing genes that should not be expressed. In addition, James et al. report that their autistic subjects had 133 percent more "inactive" glutathione in their bodies than the control subjects, and 68 percent less "active" glutathione. The researchers have since confirmed these findings in an additional 75 autistic children.

Glutathione is a crucial antioxidant needed to protect the body against the effects of heavy metals and other toxins. A deficit of glutathione leads to oxidative stress, in which rogue molecules called free radicals damage cells, leading to dysfunction or death.

The brain and nervous system are the most vulnerable to oxidative damage, a paper by the Environmental Working Group (EWG) notes, adding, "Researchers studying antioxidant protection of neurons are finding short windows during development of high vulnerability to oxidative stress."

The EWG paper notes that glutathione impairment could explain a number of phenomena associated with autism, among them:

—*The elevated vulnerability of autistic children to thimerosal*, a mercury-laden preservative previously used in many pediatric vaccines. Separate research by James et al. shows that glutathione protects brain cells from damage caused by thimerosal exposure. The researchers recently reported that cultured neuroblastoma cells contained lower levels of glutathione, and were more sensitive to thimerosal toxicity, than glioblastoma cells containing higher levels of intracellular glutathione. In both types of cells, they say, "thimerosal-induced cytotoxicity was associated with depletion of intracellular GSH [glutathione]." Pretreatment of the cells with glutathione precursors prevented damage during exposure to thimerosal.

—*The high male-to-female ratio in autism.* The report notes that women have greater antioxidant capacity than men, and that this difference is greatest in newborns. "Studies using tissue samples from newborn infants," the paper's authors note, "reveal significantly higher glutathione levels, glutathione production, and cell survival in response to oxidative stress in cells from girls compared to boys."

—*The connection between autism and intestinal disorders.* A high percentage of autistic children have severe intestinal problems and exhibit signs of "leaky gut." Glutathione is critical to proper intestinal function, appears to protect the intestines against toxicity associated with inflammatory diseases, and plays a role in preventing toxins from passing through the gut wall.

—*The link between autism and autoimmunity.* Oxidative stress, such as that caused by a deficit in glutathione, can trigger autoimmune processes by disrupting cell signaling.

James et al. have conducted preliminary research on the effects of remediating glutathione deficiency in autistic children. The researchers treated autistic children with daily supplements of the glutathione precursors folinic acid and betaine for three months, and then administered methylcobalamin (a form of vitamin B_{12}) for one month. "The intervention trial was effective in normalizing the metabolic imbalance in the autistic children," they report. While this brief study analyzed biochemical rather than behavioral outcomes, the physician administering the treatments reported improved speech and cognition in

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