Penn Researchers Find Link Between Autism and Abnormal Blood-Vessel Function and Oxidative Stress

New Findings Could Help Explain Pathology of Autistic Syndrome

(Philadelphia, PA) - Researchers at the **University of Pennsylvania School of Medicine** discovered that children with autism showed signs of abnormal blood-vessel function and damaging levels of oxidative stress compared to healthy children. The children with autism possessed levels of biochemicals that indicate the presence of constricted blood vessels via the endothelium (the cells that line vessels) with a higher tendency to form clots (through cells called platelets).

By exploring the relationship between oxidative stress and blood-vessel function in autistic patients, investigators hope to find new therapeutic options for this syndrome. The researchers, led by **Domenico Pratico, MD**, Associate Professor of Pharmacology, published their findings in the August issue of the *Archives of Neurology*.

According to the Autism Society of America, the reported number of autism cases is increasing 10 to 17 percent per year in the United States. Autism, an early onset neurological disorder, is characterized by impaired social interactions, limited verbal and nonverbal communication, and repetitive and restricted behavioral patterns. Patients with autism can differ in the severity and scope of their symptoms, suggesting that multiple factors contribute to explaining the disorder's symptoms. Previous studies at other institutions have shown that autistic patients have reduced cerebral blood flow, presumably due to constricted blood vessels in the brain, versus healthy controls.

Urinary samples of autistic children who were similar in age and healthy controls were provided by the Pfeiffer Treatment Center, where patients were diagnosed with autism disorder and evaluated. Patients were excluded from analysis if they had ever received anti-oxidant treatments or medicine with any known anti-oxidant effect; if they suffered from chronic illnesses, such as depression, psychosis, or inflammatory disorders; and/or if they were sick at the time of the sample collection. These strict criteria resulted in the small sample size in this preliminary study: 26 children with autism and 12 healthy controls.

Pratico's team measured isoprostane, a biomarker for oxidative stress; thromboxane, an index of platelet activation; and prostacyclin, a measure of blood vessel activation in the samples. "This study represents the first observation that the rates of thromboxane and prostacyclin synthesis are both not only significantly increased in autism, but are closely correlated with the rate of oxidative stress," says Pratico. Compared with controls, children with autism had significantly higher urinary levels of isoprostane, thromboxone, and prostacyclin. Oxidative stress is the result of an excessive formation of chemically unstable byproducts, called free radicals, within the cell. Under normal conditions, the cell is able to destroy the free radicals. However, when excessive free radicals accumulate, these molecules mount an attack against the cell in search of chemical stability.

"During oxidative stress, it is as if the free radicals have only one leg," explains Pratico. "They are searching for the second leg in order to keep from falling. Unfortunately, the ability of the excessive free radicals to reestablish their chemical equilibrium comes always with a price for the organ -- irreversible cellular and organ damage." Free radicals can damage cell membranes, proteins, and genes by oxidation -- the same chemical reaction that causes iron to

rust.

Pratico and colleagues measured levels of isoprostane, the chemical byproduct of free radicals attacking fat cells and found that patients with autism possess nearly double the level of oxidative stress than that measured in healthy controls.

The samples from autistic patients also revealed a biochemical imbalance in the patients' blood vessels, resulting in high levels of thromboxane - an indicator of platelet activity - and prostacyclin, an indicator of constricting endothelial cells. During normal function, thromboxane and prostacyclin work together to maintain the integrity of vessels. In response to different kinds of stress, platelets release thromboxane, which causes vessels to contract. The endothelium responds to elevated levels of thromboxane by releasing prostacyclin. This event counterbalances the effect on vessels, inducing dilation of the vessel and, in turn, more blood flow.

Autism is a complex neurological disorder and oxidative imbalance is one feature of the autistic syndrome. Several lines of evidence support the hypothesis that oxidative imbalance may also play a role in this disease: autism is characterized by an impaired anti-oxidant defense system, higher free-radical production, and improvement of behavioral symptoms after taking anti-oxidants.

"In general, it is known that abnormalities in blood vessels can be clinically reflected by an abnormal blood flow," says Pratico. "In this regard, it is interesting that earlier neuroimaging studies of autistic children have demonstrated a reduced amount of blood reaching the brain. Shedding more light on the relationship of oxidative stress and blood-vessel health to the pathology of autism could lead to improvements in therapy."

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