HYPOTHESIS: Two ways in which cytomegalovirus carrying male germ cells may play a role in the genesis of autism spectrum disorder

By

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Recently a paper was published showing that 33 of every 10,000 children born to older men (40 years of age or older) have autism spectrum disorder compared to 6 of every 10,000 children born to younger men (<30 years of age). Excerpts from a report in *Nature News* titled "**Male biological clock possibly linked to autism, other disorders**" will help flesh this out:

"In a study of more than 100,000 people, along with records about their parents' ages, Avi Reichenberg at King's College London and his colleagues found that 33 out of every 10,000 offspring of men 40 years or older had autism spectrum disorder—a 475% increase compared to offspring of men younger than 30, who fathered afflicted children at a rate of 6 per 10,000 (*Arch. Gen. Psychiatry* **63**, 1026–1032; 2006). This association is now being tested in a larger study, says Reichenberg. A study this September showed a similar but less pronounced association of parental age with bipolar disorder (*Arch. Gen. Psychiatry* **65**, 1034–1040; 2008).

"Spontaneous mutations can arise in both sperm and eggs. As women age, for example, they have an increased risk of delivering a child with Down's syndrome and other disorders caused by large-scale chromosome problems in eggs, such as trisomy. But unlike eggs, sperm arise from stem cells that continuously divide—about 840 times by the time a man is 50 years old (*Cytogenet. Genome Res.* **111**, 213–228; 2005). The theory is that the chances of mutations increase with each round of DNA replication—a process that could underlie estimates that the mutation rate in males is about five times that in females (*Nature* **416**, 624–626; 2002).

"Any mutation you can think of occurs more frequently in the sperm of older men," says Sebat.

For a very long time it was thought mutations associated with the passage of time was something primarily peculiar to the ovum (A woman's unfertilized egg). The belief that the genetic material in male sperm was somehow spared age-related mutations was driven home to me by a stem cell biologist I interacted with from 2008 to 2010, who was convinced that the male body had mechanisms in place that help insure that few if any mutations wound up in mature male sperm in healthy males regardless of age. This struck me as wishful thinking and I was quick to lock horns with this chap over this. Now comes tentative evidence – again, the results of the study just announced (above) – that would appear to vindicate my position. Although it is always fun to be right, I got to wondering what other players besides normal aging might be producing mutations in at least some men's semen that set the stage in their progeny for the development of autism and other neurological conditions. The first thing that popped to mind was pathogenic microorganisms – especially viruses. A quick check of published research brought up one particular bit of research that seemed to signal I was on the right track:

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3143078/pdf/2042-4280-2-7.pdf - "Detection of human cytomegalovirus in motile spermatozoa and spermatogenic cells in testis organotypic culture"

The long story short with respect to this study is that it found HCMV in male germ cells from semen samples (91 fertile and 47 infertile men) and in testis tissue culture. There was a decrease in the number of immature germs cells that is believed attributable to the HCMV. In short, the presence of the HCMC in a man's reproductive tract – and, mind you, 50-80 of every 100 Americans harbor the HCMV according to the CDC – tosses a monkey-wrench in the genetic apparatus of sperm resulting in infertility. There are undoubtedly other viruses that populate the male reproductive system including others of the herpes family that may well have a similar effect.

What if the genetic changes go beyond infertility? What if HCMV produces genetic mutations in fertile men's sperm? Some of these, I conjecture, could set the stage for producing autism in children they father.

Now – and here is where my off-the-cuff theorizing gets really interesting – what would happen if a HCMV-infected spermatozoon fertilizes a female ovum? In some instances it becomes activated and effects varying damage to one or more developing fetal tissues/organs including the brain and even generates defects severe enough to result in miscarriage. However, what I propose is that most HCMV transmitted to a fetus at conception by an infected male germ cell (sperm) is latent (inactive)and winds up in various tissues though primarily the CNS [The virus preferentially infects neurons probably brain stem & progenitor cells too (This is the case in mouse models of CMV infection)]. Though not active in the sense it produces clinical symptoms it could conceivably cause subtle neurologic changes and damage that is later manifest as autism spectrum disorder (One murine study notes: "Infection of neurons may tend to become persistent by evasion of immune reactions, anti-apoptotic effects and neuron-specific activation of the e1-promoter, presumably causing functional neuronal disorders. It has also been shown that CMV infection in developing brains may become latent in neural immature cells". These effects were observed in active infections. However, it may affect subtle genetic damage in neurons in a child's developing brain though the virus is latent or largely inactive).

This body of conjecture is testable. And, if it turns out HCMV is damaging some men's germ cell DNA in ways that set the stage for autism (and possibly other neurologic disorders) in children they father and/or the virus is being passed on to zygote (by the male gamete) and ultimately the embryo's developing CNS where it sets the stage for the development of autism or other neurologic disorders years after birth, testing for the HCMV's presence in semen and (when determined to be present) interfering with the HCMV in the man's reproductive tissues by treating with extant antiviral drugs are measures that might reduce the likelihood the virus will wreck biologic havoc either in the developing embryo or later in the developing baby or child.

I hope some enterprising grad student or researcher transforms my ruminations into suitable bench experiments and runs with it.

Additional Reading: This paper titled "Neuropathogenesis of Congenital Cytomegalovirus Infection: Disease Mechanisms and Prospects for Intervention" delves deeply into technical issues I only touched on above as well as prevention and treatment aspects of HCMV infections.

 If you are a grad student or researcher who runs with one or both of the ideas articulated above, please let me know what you do and the outcome: attachi-mailbox@yahoo.com