

Autism and VCFS: News and Views

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A recent news release from the American Academy of Child and Adolescent Psychiatry (AACAP) dated September 20, 2013 stated the dramatic headline, "UC Davis Study: Half Of Kids With 22q May Be Misdiagnosed As Autistic." This conclusion was reached by research team at the University of California's M.I.N.D. Institute that has been very active in VCFS research under the leadership of Tony Simon, Ph.D. This headline actually came from a news story broadcast by the CBS affiliate in Sacramento and quoted Kathy Angkustsiri, an assistant professor at the UC Davis MIND Institute and a published researcher in the field of VCFS investigations. A recent report from Angkustsiri and colleagues¹ is actually quite important, going beyond the study of VCFS with implications for the entire field of autism. One would have to be living in a concrete bunker isolated from the rest of the world to be unaware of the recent statistics related to the frequency of "autism" in the general population. Just a few years ago, we were bombarded by public-service announcements on television and radio citing reports that one in everyone and 125 people were autistic, then one in every 88 people (a number reported by the CDC) and now some estimates are 1 in 50. One in 50? Holy cow! If we go to a baseball game at Yankee Stadium, are 1000 people with autism in the stands?

Why Is There So Much Autism?

We used to know what autism was. All of us graduated from university a long time ago. We learned that autism, a term first coined in 1910 by Bleuler,² was first used to describe symptoms consistent with schizophrenia, derived from the Greek

to mean self-absorption. The study of autism as a developmental disorder and its early delineation was introduced by Leo Kanner in 1943.³ Kanner, often acknowledged to be the founder of the field of child psychiatry, was followed by Bruno Bettelheim of the University of Chicago who became a champion of research and publication in autism, adopting a theory that stressed nurture as a more important factor than nature as the cause of autism.⁴ What is clear is that many of the children who today are diagnosed as being autistic would never have been recognized by Bettelheim, Kanner, and others of their generation as being “autistic.” The definition of autism began to expand to explain phenomena such as social awkwardness, withdrawn behavior, a variety of cognitive peculiarities, and, in some circumstances, behavior that was not at all abnormal, especially in children who had cognitive impairments or early histories of chronic illness. The diagnosis expanded to “autistic-like” behaviors, “Autism Spectrum Disorder,” and included previously distinct disorders including “Asperger’s syndrome” and “Pervasive Developmental Delay.” How could that happen under our very noses?

Distinguishing a Neurological Disease, a Neurodevelopmental Disorder, a Sign, and a Syndrome

The word “disease” can have a variety of definitions depending on context, but in the world of medicine, a disease has a distinct meaning. According to the Oxford Dictionary, a disease is: a disorder of structure or function in a human, animal, or plant, especially one that produces specific signs or symptoms...and is not simply a direct result of physical injury. The key here is that a disease causes progressive signs and symptoms. In other words, when a person has a cold (the disease), the symptoms include sneezing, congestion, coughing, runny nose, etc. Sneezing is not a disease, it is a symptom (and it is not progressive). While all colds result in sneezing, not all sneezing is the result of colds. People sneeze from allergies, something tickling their nose, or sinusitis. Diseases have direct causes. In the case of a cold, it is a virus that infects the mucus membrane of the upper respiratory tract. So, what is autism? Is it a disease, a developmental disorder, a symptom or group of recognizable signs and symptoms?

Being more specific, because many people believe there are numerous genetic causes of autism, we can look at what genetic syndromes are. An international working group was convened in the 1980s to deliver a consensus opinion about a definition for a syndrome. They did so, coming up with a simple, yet inclusive definition that has stood the test of time. A syndrome was defined as multiple anomalies in a single individual with all of those anomalies having a common cause. An anomaly is simply something, either physical or behavioral, that is considered to be abnormal. Tetralogy of Fallot and cleft palate are physical anomalies, learning disabilities and ADHD are behavioral anomalies because

they are assessed by what the person is doing, rather than a physical measurement or biochemical laboratory test. Velo-cardio-facial syndrome is a syndrome because the observed anomalies in a single individual with VCFS such as cleft palate, congenital heart disease, learning disorders, immune disorders, hypotonia, speech problems, psychiatric issues, etc. would not be present in that individual were it not for the specific deletion of DNA from chromosome 22q11.2. Any one of these anomalies can occur in individuals who do not have that deletion, but they will not occur in the same recognizable pattern with the same predictable outcome. For example, if we simply list congenital heart disease, “developmental delay,” feeding difficulties in infancy, and palate abnormalities, we could find dozens of syndromes with those same findings, such as Down syndrome, fetal alcohol syndrome, Apert syndrome, CHARGE syndrome, Cornelia de Lange syndrome, and Melnick-Needles syndrome to name only a few. However, no one would confuse these other syndromes with VCFS because the pattern of the full range of anomalies and even the overall appearance of such cases is dramatically different. Moreover, each has a completely different cause unrelated to chromosome 22 deletions. They are all syndromes, but they are different syndromes from VCFS.

So, disorders, diseases and syndromes have specific causes, and a range of signs and symptoms. Among those signs and symptoms are behavioral anomalies consistent with autism (functional impairment in natural play, socialization, and language). All of the signs and symptoms consistent with the diagnosis of autism are behavioral. None are physical. How is autism diagnosed? At the non-standardized level (meaning based on observation alone), autism is diagnosed by listing observed features, or symptoms derived from histories obtained from parents, and determining if those symptoms are consistent with what the examiner considers to be autism. At the standardized level, the diagnosis is made using a predetermined list of signs and symptoms from parental questionnaires that have been accepted by the research and academic community to be rigorous and thorough assessments based on observation, history, and probing questions. One such test is the ADOS, the **A**utism **D**iagnostic **O**bservation **S**chedule, and similar commercially available instruments, all of which are similar in terms of their methods. The ADOS (now the ADOS-2), first devised in 1989 by Catherine Lord and colleagues⁵ is a series of tasks that involve interaction between the examiner and the person being tested that allow observations of behavior. Those observations are then plugged in to categories listed on the score sheet. These responses are then counted with the score being compared to established “norms” and that score is used to determine the diagnosis. Is this a valid approach? For example, let us apply this same method to sneezing, congestion, coughing, and runny nose on a mythical test called the CDOS...the **C**old **D**iagnostic **O**bservation **S**chedule. The test provides these as

categories to check off, and if three out of four are present, you have a cold. Of course, if it is September in New York State and the goldenrod and ragweed are in bloom, it may be allergic rhinitis and what we used to call “hay fever.” The basic principal of the ADOS and similar tests is that symptoms = a disorder or disease, or symptoms are indicative of a disorder or disease. This is a principal with which we strongly disagree because disorders, diseases (and syndromes) are only present when the causes are present and the cause is correctly identified. Without the virus, there is no cold, without the deletion, there is no VCFS.

What is autism? As we understand it today, autism is a group of signs and symptoms, not a disease. Autism is a group behaviorally defined neurodevelopmental disorders—most of which probably have a genetic basis. The unusual behaviors that were initially (and still are today) considered to be hallmarks of autism may not have a specific cause. These signs of autism include stereotypical behaviors (arm flapping, rocking, head banging, etc.), cognitive deterioration, repetitive behaviors, compulsive behavior, resistance to change, rituals, and some self-injurious behaviors. For parents of children with VCFS, at least some of these signs and symptoms sound familiar. Although stereotypic behaviors are not very common in VCFS, repetitive behaviors are, compulsive behaviors are, resistance to change, and skin or nail picking, scratching of sores and other behaviors that might be considered to be self-injurious, are also common. So, does this constitute autism?

If the definition of autism is a score on a checklist or the number of positive symptoms consistent with what has been defined as autism, then many children with VCFS will probably qualify for the diagnosis. In a paper published in 2006, Vorstman et al.⁶ reported that 50% of a sample of 60 children with VCFS qualified for the diagnosis of autism spectrum disorder. This report was criticized in print by Eliez in a Letter to the Editor of the same journal,⁷ and at the annual meeting of The Velo-Cardio-Facial Syndrome Educational Foundation in Strasbourg in 2006 by both Dr. Eliez and others, including authors of this editorial. The gist of the criticisms were that the behaviors seen in children with autism (meaning what anyone would recognize as autism) do not resemble what is seen in children with VCFS except in rare cases. Eliez reported that autistic behaviors, specifically as they relate to communication, were seen in only 3% of his sample of 300 children with VCFS. Eliez also expressed concern about drawing potential clinical and treatment implications to management, especially in relation to gaze avoidance, verbal skills, and approaches to social situations that he thought were incompatible with proper management in VCFS. Vorstman replied to Eliez’ response, stating, “...we appreciate the comments brought forward by Eliez. We do believe, however, that he has not presented convincing arguments to dismiss our finding of a high prevalence of ASD in 22q11DS.”⁸ The collective experience of the authors of this editorial is expansive

and includes well over 1,000 cases and we cannot agree with the conclusions of Vorstman et al.

Does autism occur in children with VCFS? If we focus in on what we truly know to be autism, then the answer is yes, but it occurs with very low frequency and in the case of VCFS, we understand the reason why the symptoms occur. VCFS is a neurodevelopmental syndrome with a wide range of cognitive and behavioral disturbances that overlap with some of the features of autism. However, the number of cases of VCFS comprise a very, very small percentage of children who meet the current criteria for a diagnosis of Autism Spectrum Disorder. For most of the children who truly qualify for the diagnosis of autism, there is still no specific identifiable biological cause. There have been many studies that have attempted to isolate genetic contributions to autism or specific brain anomalies, but to date, there is no solid evidence for a single or specific cause for all, or even most cases of autism.

We have heard from many parents of children with VCFS who have been given the diagnosis of autism that even though they realize that the diagnosis may not be the most appropriate label, they are glad to have it because it will give their children access to additional services. But what kind of services? Eliez has pointed out that treatments for children with true autism may not be advisable or applicable to children with VCFS.⁶ Moreover, there is often very good management of learning, social and behavioral disorders in VCFS that fall outside of the realm of autism management. The entire purpose of an accurate diagnosis is more effective treatment. More treatment is of no advantage if the treatment is not specific to the disorder.

Sensitivity and Specificity

In explaining the burgeoning rate of autism diagnoses in the general population, one has to scratch their head and wonder why this is occurring. One possible explanation is that autism is really on the rise. If that is the case, then with a reported prevalence of one case per 50 children, we would expect the birth rate to drop dramatically. This is actually not meant to be a facetious comment. That number is scary! Even at face value, most people would probably find it difficult to accept. Of course, if one accepts this increase as fact, it is natural to wonder about the causes. The public has been exposed to many hypotheses including the use of thimerosal as a preservative in childhood vaccinations. The outcome was that many parents chose to avoid inoculating their children against potentially dangerous diseases such as measles, mumps, varicella, and pertussis even in the face of large studies that showed no link between thimerosal preserved vaccines and autism.⁹ The risk of making spurious assumptions or correlations can be dangerous.

Another explanation is that the rate of autism has always been high, but we are just recognizing it now. This seems unlikely given the intensity of study of autism over the years, including the major efforts begun in the 1960s because of the attention spurred by the work of Bettelheim and others.

Another explanation is the expanding scope of what is considered to be autism. There is little doubt that this is happening. Diagnostic criteria are constantly shifting as demonstrated by the recent release of the DSM-5 guidelines. There are major differences between the Diagnostic and Statistical Manual of Mental Disorders in its fourth version (DSM-IV) and its most recent version (DSM-5). Perhaps the reason is that diagnoses that depend entirely on behavioral signs and symptoms are not actually describing specific disorders or diseases, but rather symptom groups that are not necessarily specific to a single cause.

The last possible explanation is that the diagnostic tests currently being used are overly sensitive and not very specific. Diagnostic tests require high sensitivity (detecting a disease when it is present) and high specificity (making sure the diagnosis is identifying the correct disease). It is possible for tests to be too sensitive and not very specific. Perhaps this is the case with the current diagnostic battery for identifying autism.

Causality and Psychiatric Issues

It is interesting to find VCFS as a specifier for ASD. In fact VCFS, having a known cause, is a disease entity, unlike most DSM “disorders,” and commonly presents with some symptoms that are also criteria for ASD, as well as bipolar disorder, several anxiety disorders, major depressive disorder and schizophreniform disorder.

The fact that some or many VCFS cases are misdiagnosed as ASD might be useful as far as access to services is concerned, but does not guarantee that these services are appropriate, evidence-based and developmentally appropriate. As VCFS cases appear to manifest a variety of developmental and cognitive-behavioral disturbances, rather than trying to fit VCFS into ASD or Childhood Schizophrenia, we should focus on what VCFS is teaching us about psychopathology, learning, psychosis and development. We must also keep in mind that in many VCFS cases, early speech, verbal and learning issues can follow traumatic childhood years with extensive medical treatment, hospitalization, anxiety disorders, and the inherent developmental delays. Culling out the pathogenesis of anxiety disorders, especially separation and social anxiety disorder and its association with executive function deficits can often lead to social isolation, withdrawal, regression and cognitive decline. These findings overlap with diagnostic criteria for autism checklists.

At different times, VCFS cases can meet a variety of diagnoses, but the only diagnosis they actually have is VCFS. They might meet criteria, at different times, for

different diagnoses. The variety of developmental, neuropsychological and behavioral disturbances in VCFS of developing one of three psychiatric diagnoses: Schizophrenia, Bipolar Disorder or ASD makes VCFS the Copy Number Variant (CNV) most likely to predict psychiatric illness. Its manifestations are DSM scientists' nightmare. They cut across internalizing, externalizing, neurotic, psychotic, anxiety, autistic, mood, schizophrenic disorders, learning disorders and intellectual disability.

Summary

In many clinical settings, the core components of autism spectrum disorder that often lead to the diagnosis are typically three findings as stated earlier: relative deficits in communication and language; socialization deficits; and abnormal play skills as a young child. These are all broad and relative neurological deficits that are behaviorally defined. Many years ago, these were called “soft signs” of underlying neurologic abnormalities. The breadth and vagaries of these core components open the floodgates to allow up to 2% of all children to fall into the ASD spectrum, and these core components are present in most children with VCFS. If we continue to allow broad categories of persons who are just different in their neurologic function and ability to fit a diagnosis, there will be labels for broad nonspecific groups of people yet to come. This same phenomenon is being observed for ADHD and learning disabilities where diagnoses have more than doubled over the years. VCFS overlaps all of these conditions, and the number of diagnoses that can be attached to children with the syndrome continue to expand.

Conclusion

The recent announcement from AACAP prompted by our friends at the MIND institute at the University of California, Davis is an important one and could have broader implications than those related to VCFS. Let us hope so.

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