Editorial Commentary

Behaviorally associated changes in neuroconnectivity following autologous umbilical cord blood infusion in young children with autism spectrum disorder

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Autism spectrum disorder (ASD) is a behaviorally defined neurodevelopmental disorder that now affects almost 2% of children in the United States (US). Although ASD is a very heterogeneous disorder with many associated psychiatric and medical co-morbidities (1), specific core symptoms define its diagnosis. ASD is defined by a deficit in social-communication along with the presence of repetitive and/or restricted interests and/or behaviors. ASD is a relatively new medical disorder, first described by two practitioners, Leo Kanner and Hans Asperger, in the 1940s, it was not recognized as its own disease in the Diagnostic Statistical Manual of Mental Disorders (DSM) until 1987 (2). Since then it has gone through several revisions in its definition. In the 4th edition of the DSM it was divided into three distinct categories, only for these subcategories to be dropped in the 5th edition of the DSM in lieu of being consider one disorder on a spectrum depending on levels of supports needed for the individual to function.

The history of the evolving and fluctuating definition of ASD is in no doubt driven by the fact that the etiology of ASD is still largely unknown. The fact that ASD appears to have a highly heritable component has driven research into genetic causes of ASD (3). However, empirical clinical studies have not supported a strong genetic component. In fact inherited single gene and chromosomal defects seem to only account for a minority of ASD cases (4) and studies pointing to single-gene disorders find that these mutations are rare *de novo*, not inherited, mutations (5,6). Thus, it is becoming clear that ASD arises from complicated interactions between genetic predisposition and environmental factors (7,8). Recent reviews demonstrate that there are numerous environmental agents and prenatal factors that increase the risk of ASD (9).

As research in ASD has evolved, studies focusing on non-genetic physiological factors, including mitochondrial dysfunction, redox metabolism, immune dysregulation and inflammation, have grown rapidly over the last two decades (3). What is exciting about this non-genetic research is that identification of physiological targets opens the promise to the development of effective therapies for ASD. This type of research is critical as currently effective treatments for ASD, especially those that target underlying biological pathophysiology, are absent, creating a significant unmet need for the millions of individuals who suffer from ASD.

At this time, the standard-of-care treatment for core ASD symptoms is a combination of behavioral therapy such as applied behavioral analysis (ABA) combined with educational and other rehabilitation therapies such as occupational and speech therapies. Behavior therapy requires full-time engagement with a one-on-one therapist over several years starting early in life (10,11) but, unfortunately, can be difficult to obtain since it is not

covered by many medical insurers and is not available in the education system in many states (12,13). Even when applied in a consistent manner, many times behavioral therapies results in incomplete recovery (10) and life-long supportive care into adulthood is required (14).

At this time, the only US Food and Drug Administration (FDA) approved drugs for ASD are atypical antipsychotics. These medications have an indication for a serious behavioral problem associated with ASD called irritability. However, these medications do not target core symptoms of ASD and do not positively influence the underlying pathophysiology of ASD, thus they merely treat symptoms without affecting the disease process. These medication have significant adverse effects, particularly troublesome is their negatively effect on lipid and glucose metabolism and body weight (15-17), increasing the risk of cardiovascular disease and type-2 diabetes (18) and potentially causing tardive dyskinesia, a serious movement disorder (19).

Thus, an effective treatment, especially one that is safe and targets underlying pathophysiological processes could substantially change the course of the lives of many children and their families who are affected by ASD. At our center we have concentrated on correcting metabolism disruptions because of the significant safety profile of the treatments (20). However, more and more evidence has pointed to the importance of the immune system as an important etiological factor and ongoing physiological disruption in individuals with ASD (21). However, one major problem in addressing immune system abnormalities is that immunological treatments have a high adverse effect profile (22).

In the paper by Carpenter *et al.* (23) the authors investigate the novel treatment of autologous umbilical cord single-infusion in a Phase I clinical trial. Animal models suggest that such therapy positively influences the immune system by suppressing inflammation. Preliminary data suggest that this therapy is well-tolerated without significant adverse effects and may improve core symptoms of ASD including social function and communication. This type of pioneering study is of the upmost importance at this time since non-FDA regulated forms of "stem-cell therapy" are being marketed and offered both inside and outside the US, with little guidance as to whether the therapy is safe and effective. Families desperate for effective therapies for their children will sometimes use such treatment centers with only hope that the treatment will work. Although Carpenter *et al.* (23) has taken the first step to investigate this promising therapy both Phase II and III clinical trials, some of which are underway in the US (NCT02847182[1]), will be needed in order to confirm the safety and efficacy of this novel treatment. We can hope that families will await the critical guidance that such studies can provide before embarking on therapeutic regimes prematurely. The investigators have even launched an expanded access protocol to increase the availability of umbilical cord blood infusions to selected patients (NCT03327467[1]).

As previously mentioned, ASD is considered a spectrum leading to considerable heterogeneity in the population and leading to many challenges when conducting clinical trials (24). Individuals with ASD have large variation in intellectual development and many have common medical co-morbidities (24). Heterogeneity sometimes can be mitigated by selecting participants to match their outcome measure. For example, antipsychotic drug trials have targeted highly irritable individuals with ASD since their primary outcome measure was irritability (25). However, being preliminary, the Carpenter *et al.* (23) study was exploratory in regards to outcome measure and aimed to target general aspects of ASD. Furthermore, open-label uncontrolled trials, such as Carpenter *et al.* (23), need to be considered cautiously especially due to the significant placebo effect seen in some clinical trials in individuals with ASD (2). Unfortunately, it has not been uncommon for controlled clinical trials to fail because they were based on outcome measures validated in open-label uncontrolled trials which did not account for many important factors that added bias and variability (24).

To surmount the limitations of previous studies Carpenter *et al.* (23) took a very innovative approach to validating the outcome measures. Building on previous research that suggested that autologous umbilical cord can alter neuroconnectivity, the research team used magnetic resonance imaging to obtained diffusion-weighted images of the brain before and 6 months after treatment with autologous umbilical cord blood for 19 of the 25 participants enrolled in the clinical trial. White matter connectivity between brain regions known to be important for the abilities measured as outcomes, specifically the frontal and temporal cortices and subcortical regions, were calculated. Three outcomes measures were then used to judge change in symptoms with each outcome measure obtained from a different observer

[1] This number refers to the clinical trial registration number that can be used to locate the specific study on the clinicaltrials.gov website.

in order to ensure that there was consensus in outcomes. The Vineland Adaptive Behavior scale is a parent reported measure in which social ability was assessed. The Clinical Global Impression scale is a judgement of overall ASD symptoms as assessed by an experienced ASD researcher. Lastly, the Expression One-Word Picture Vocabulary Test is a clinician conducted assessment. The change in these three outcome measures were then correlated with changes in connectivity between selected brain regions. To reduce the type I error rate, the authors report only regions of the brain in which statistically significantly correlated with at least two outcome measures.

Ten pairs of brain regions were found to have connectivity which was significantly related to the outcome measures based on this criterion. The authors then investigated if any of these relationships could be accounted for by age or baseline general cognitive abilities. Four of the relationships were found to be related to the participant's age with all four losing criteria for being significantly related to outcomes. Three of the relationships were found to be associated with overall cognitive level, with two of these relationships losing criteria for being related to the outcome. Thus, four pairs of brain regions remained related to the outcome measures after accounting for these potentially confounding factors.

Thus, this study identified some of the clinical symptoms and the potential related neurobiological mechanism that were altered following a clinical treatment with autologous umbilical cord blood. Despite demonstrating the relationship between change in behavior and development and change in the neurological pathway, it is important to remember that without proper controls it is not possible to specifically say that these changes were due to the treatment *per se*. Indeed, designs such as a 6 months observation period prior to the treatment baseline or a sham run-in period where behavior and development and neuroimaging measures are obtained at one or more points before the baseline may have allowed an assessment of the changes that occurred after the treatment in order to determine which changes may have been natural (or due to placebo) and which changes were specifically due to the treatment. Never the less the data does provide some validated target outcome measures which are related to neurological changes within the study design and participant population.

It should also be remembered that correlation statistics only work well when there is a broad range of values. This reminds us that the changes in the outcome measures and change in brain connectivity were probably very variable, participant-to-participant (the means, standard deviations and scatterplots are not presented in the paper). This is important as it reminds us that there were different levels of behavioral and neurological development over the 6 months period, potentially due to variability in the response to treatment. This is a very important aspect to the study that needs to be addressed and examined in detail since ASD is truly heterogeneous. Thus, it is expected that there are probably many underlying etiologies which cause ASD which will respond to different treatment. Further research examining baseline participant characteristics or biomarkers which can select the individuals which are most likely to respond would be a great addition and help understand how to most effectively apply this therapy. Indeed, determining the most effective therapy for the large number of children with ASD in a personalized, precision medicine approach will greatly improve the efficiency of medical care for children with ASD in the future.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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