REVIEW PAPER

AUTOLOGOUS CORD BLOOD TRANSFUSION FOR CHILDREN WITH AUTISM SPECTRUM DISORDER

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A. BACKGROUND

1. Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder with symptoms beginning early in life. The Diagnostic and Statistical Manual for Mental Disorders, 5th Edition (DSM-5) provides clear diagnostic criteria for ASD (impairments in social communication and interaction, with restricted, repetitive behaviours).[1] In the USA, the estimated prevalence is 1 in 68 children. It is 4 times more common in boys. The prevalence in Singapore is estimated to be 1%, although no formal prevalence studies have been conducted. Approximate 20% of the preschool children seen in the Child Development Program (CDP) run by KK Women's and Children's Hospital and National University Hospital are diagnosed with ASD.[2] The actual number of affected preschool children diagnosed through the CDP has been increasing over the years, from 508 children in 2004 to 1031 children in 2017. There are no data on the number of children diagnosed in the private sector. The Ministry of Health's (MOH) Burden of Disease Study in 2010 showed that ASD was the third leading cause of disease burden from mental health disorders in Singapore and the leading cause in children under 15 years of age.[3]

2. Children with ASD usually need more resources than neurotypical children. With the increasing number of children diagnosed over the year, the demand for special schooling has increased. There are no published data on the number of children with ASD in special schools, as not all affected children attend autism-specific special schools. St Andrew's Autism School for children with moderate to severe ASD saw its intake increase by 13.1% between 2016 and 2017.[4] The number of students in the Eden School, a special school also for children with moderate to severe ASD, increased from 138 in 2010 to 313 in 2016.[5] These 2 schools, together with AWWA Special School, needed to increase their capacity for children with ASD by 75 places in 2017.[6] Pathlight School, which mainly supports children with ASD who are able to access a mainstream syllabus, doubled its total enrolment from 603 children in 2010 to 1269 children in 2017.[7] The number of students with ASD in mainstream school has also increased from 3500 in 2012 to 5000 in 2016.[8] These children often require assistance from the support services in their primary and secondary schools. Together but indirectly, these data show the increasing amount of resources that children with ASD in Singapore require.

3. There are currently no curative treatments for ASD. Symptom reduction is achieved by behavioural therapies and social communication support. As affected individuals can also have comorbid mental disorders (anxiety, depression and Attention Deficit Hyperactivity Disorder), pharmacological treatment may also be required. Overall, the burden of disease can be very high for individual families and the quality of life can be significantly impacted. Unpublished data from the Department of Child

Development in KKH showed that almost 30% of parents of children with ASD reported clinical levels of depression.

4. Part of the reason why curative treatments currently do not exist is the complex and heterogeneous etiology of ASD. It is highly heritable, but with complex and highly variable genetics[9] and affected by epigenetics.[10, 11] Prematurity[12] and birth hypoxia[13] have been associated with ASD.

B. THE CENTRAL NERVOUS SYSTEM CHANGES IN ASD

There is no doubt that ASD is a neurodevelopmental disorder. Numerous studies have shown a variety of changes in the brain, including decreased or altered connectivity, hypoperfusion and immune deregulation.[14] Increased plasma cytokine levels, localised inflammation and pathological astrocyte overgrowth have also been found in ASD.[15] Both post-mortem brain tissue studies and PET imaging data from living individuals with ASD have shown evidence of increased microglial activation, suggesting that immune and/or inflammatory-mediated brain damage play a role in its etiology.[16.]

C. AUTOLOGOUS UMBILICAL CORD BLOOD (UCB) TRANSFUSION AS A THERAPEUTIC OPTION FOR ASD

(1) Background

With the current evidence suggesting that there is an immune pathology in ASD, therapies targeting immune modulation have been considered. UCB cells have been shown in vitro to be able to protect neuronal cell cultures (oligodendrocytes and astrocytes) from damage induced by hypoxia/ischemia.[17] A non-randomised, open label, single centre Phase I/II trial was conducted in China to investigate the safety and efficacy of combined transplantation of human cord blood mononuclear cells and umbilical cord-derived mesenchymal stem cells in 37 children with ASD with ages ranging from 3 – 12 year of age.[18] There were statistically significant differences in the Childhood Autism Rating Scale, Clinical Global Impression Scale and the Aberrant Behaviour Checklist. The combination of cord blood mononuclear cells and mesenchymal cells had larger therapeutic effects than the cord blood mononuclear cells alone.

(2) Safety of UCB

Although there are very few trials with UCB in children with ASD, it has been used for other paediatric conditions. Novak et al conducted a meta-analysis of UCB trials for cerebral palsy.[19] In 328 participants followed up for 6 months, serious adverse

effects were rare (3% in the study cohorts and 2% in controls). In the Dawson trial with 25 subjects with ASD described below, assessment of adverse events across a 12-month period showed that it was safe and well tolerated.[20] In the Chez trial also described below, UCB infusion in their 20 children with ASD showed no serious adverse effects compared to a saline placebo.[21]

(3) Review of trials involving UCB for ASD

There are currently only 2 published trials using Autologous UCB for the treatment of ASD.

i. In 2017, Dawson et al reported on a prospective Phase I single centre trial in Duke University involving 25 subjects with ASD of a median age of 4.6 years (2.26 – 5.97), to determine the safety of autologous UCB in children and the outcome measures that could be used as primary and secondary endpoints for future randomised Phase II trials.[20] Improvements in social communication and beneficial changes in core ASD symptoms were reported. Computerised eye-tracking assessments showed improvements in social attention and behaviour that were associated with increases in connectivity across brain regions assessed using diffusion tensor imaging.

   In 2018, Murias et al reported on the same cohort of children and showed that there were increased alpha and beta power and decreased theta EEG power.[22] Higher baseline posterior EEG beta power was associated with a greater degree in social communication symptoms.

ii. In 2018, Chez at al from the Sutter Medical Centre in California in USA reported on another single centre, randomised, placebo-controlled, blinded study with treatment crossover at 6 months involving 29 children aged 2 to 6 years with a confirmed diagnosis of ASD.[21] The aim was to evaluate the safety and efficacy of an autologous UCB infusion versus a saline placebo in these children. There was a trend towards improvement, particularly in socialisation but no statistically significant differences for any endpoints. The authors recommended that tightly controlled trials were necessary to further progress the study of autologous UCB for ASD.

(4) Trials in progress

i. A Phase II randomised, placebo-controlled, blinded crossover study is currently in progress in Duke University.[21]

ii. A Phase II, open label study is also in progress in Duke University to investigate the safety of matched, unrelated donor umbilical cord derived mesenchymal stem cells.[23]

iii. A prospective Phase I single centre trial to assess the safety and efficacy of a single infusion of autologous UCB in children with ASD is currently in progress in the Department of Child Development of KK Women's and Children's Hospital, in collaboration with Duke University.

Review of websites that record ongoing trials and studies have not shown further studies on UCB in ASD children. [24-29]

D. CONCLUSION AND RECOMMENDATION

1. Studies have demonstrated the safety of Autologous UCB transfusions in children.

2. Only one of the 2 published studies showed a definite improvement in the symptoms of ASD. Both the studies have been conducted in very small cohorts of children. There are insufficient published studies to conduct a meta-analysis.

3. Furthermore, the long term safety and positive effects of this treatment have not yet been established. Hence, further studies are required to establish its usefulness and safety.

4. At this point in time, the use of Autologous UCB for the treatment of ASD should be carried out only in a research setting, until further evidence of its long term safety and efficacy is available.

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