

Stem Cells for Autism

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When he was 3 years old, Anu and Virat's son Aarav was diagnosed to have autism. After the initial shock, they set about trying various kinds of rehabilitative therapies and several alternate ones too. Although there was some improvement, they were impatient to find a cure, and so when Anu came across an advertisement for stem cell therapy for autism in the parents' chat group they wondered whether this was worth trying. Naturally, there were many questions in their minds, and they needed further clarity before they could make a decision. What are stem cells? Would the stem cells really cure Aarav's autism? Are there any side effects or other risks involved?

What is Autism?

Autism Spectrum Disorder (ASD) or autism, is the term for a group of conditions which have similar behavioural symptoms that appear early in childhood. These behaviours can be broadly grouped into those due to communication deficits and repetitive sensory-motor behaviours. Symptoms vary in severity, and affected individuals can be placed on a spectrum depending upon the extent of support they need. The condition is not uncommon and it is a fact that it is more prevalent now than in the past two decades [1]. Scientific research has provided many insights into it (although it is not completely understood), and the outlook for affected individuals is much more optimistic than it was 50 years ago [1]. Many are able to live productively in their communities, and some show significant improvement by adulthood. A subset of individuals, however, are unable to live independently and require support, putting their families under social and financial pressure.

The precise cause for autism is not yet known. Several contributory risk factors - both genetic and environmental - have been identified. There is, so

far, no cure for it, and a few symptomatic treatments are the only recourse that parents have [2]. In such a scenario, numerous alternative therapies have been tried with little success. In recent years, stem cell "therapy", although still experimental, is being increasingly offered as a treatment for autism.

What are Stem Cells?

Human bodies are made up of trillions of cells of different types and functions. Stem cells are the "parent" cells found in almost every organ of the body which can give rise to other cell types with specialized functions, such as liver cells, blood cells, brain cells, etc. In the early developing embryo, stem cells (called embryonic stem cells) can form almost all specialized cell types found in the body, but stem cells in adults have a much more limited capacity to form specialized cells. As a rule, adult stem cells can only give rise to cell types of the organ they are found in. For example, stem cells in the brain can only form the different types of brain cells. The bone marrow has two main types of stem cells- one which forms bone, cartilage and fat and the other forms blood cells.

Since stem cells can form new specialized cells, stem cell therapies aim at regenerating or replacing cells that are affected by disorders and diseases. This can be done by removing stem cells from the patient or a donor and making them into the desired specialized cells in a laboratory (by adding reagents known as growth factors) before transplanting them back into the patient. Another method is to take out stem cells from a patient's body, remove and discard other unwanted cells and inject the remaining stem cells back into the patient, in the hope that they will migrate toward the damaged organ. This could happen because in the damaged tissue are found certain molecules that can attract the stem cells. Not only that, once they reach the damaged site, various

molecules like growth factors can transform the stem cells to the specialized types of cells required to replace the lost cells. This has been observed in studies on animals like rats [10].

Causative Factors for Autism

To re-iterate, the precise cause for autism is still not known. Several contributory risk factors have been identified including both genetic and environmental factors and the interaction of these. Genetic studies of autism have identified mutations (variations) that interfere with typical brain development of the fetus during pregnancy and through childhood. These genetic mutations affect the connections and networks that are formed between cells in some specific areas of the developing brain, particularly those regions involved in social-emotional processing [2]. Besides this, there are some other differences between autism and neuro-typical brains, including disturbed layering of cells in the grey matter of the large cerebral hemispheres and reduced blood supply in some regions [3]. Not only are the changes in autism restricted to the brain, but there is also evidence of immune system disturbance (seen in some groups of autistic individuals, not all), intestinal disturbance, effects of exposure to toxins such as heavy metals, and hormonal imbalances. Thus, multiple systems appear to be involved in autism, making it difficult to find one treatment that works for all.

In a nutshell, autism is a complex condition and leaves many questions unanswered. So, claiming a treatment for such a condition where the cause is still largely unclear, should be done with extreme caution.

Stem Cell Therapy

Stem cell research has made rapid progress since its beginnings about 50 years ago, and currently stem cell therapy is approved and used only to treat some cancers and other disorders of the blood and immune cells [4-7] by transplanting bone marrow stem cells that form blood and immune cells to replace the diseased cells.

Clinical Trials of Stem Cell "Therapy" for Autism

Stem cell "therapy" has not been approved for autism. A few clinical trials of stem cells for autism have, however, have been carried out and published (reviewed by Price in [8]). The trials are based on a very weak scientific rationale according to Price [8], because of certain properties of stem cells. Stem cells naturally secrete some proteins that suppress harmful immune responses (inflammation) and others that are growth factors for cells around them [9]. A few also help the growth of new blood vessels and reduce death of surrounding cells [9]. So, why is the rationale weak? Firstly, it is not clear whether immune disturbances in autism have any connection to the symptoms and thus even if the stem cells had some effect on the inflammation, would it alter the behavioural symptoms or the underlying brain changes? Secondly, the immune changes are not found in all individuals with autism and there was no attempt by the clinical trials (except one) to assess immune parameters in subjects either before or after the stem cell infusion so the effect is a presumed one, if it exists at all. Thirdly, do the injected stem cells reach the brain at all, if so how many and how long would they survive? There is some evidence for this from stem cell research in rat models of autism, although it has been well established that what works in rodents does not usually work similarly for humans [10]. Even if they did reach the brain, how would a shot of stem cells alter the genetic and environment-influenced structural brain networks that have formed over several years? What about the other systemic changes seen in autism such as gut and hormonal disturbances? None of the published clinical trials have assessed these.

Various types of stem cells have been used, including umbilical cord blood stem cells and bone marrow stem cells. These have been sourced from donors or from individuals themselves. The route of administration of the stem cells is either by intravenous injection or injection into the spinal region.

In a review of clinical trials of stem cell "therapy" for autism [8], as of December 2019, there were 13 clinical trials of stem cell therapies registered on clinicaltrials.gov (the official National Institutes of Health, USA, clinical trials registry). Of these, seven were completed. Of the completed and published trials, only one was a well-designed, controlled clinical trial. A controlled clinical trial is one which includes a group of similar subjects for comparison, who are either treated with a placebo (a substance that is inert or has no therapeutic effect) or not treated at all. This one trial showed no significant benefit of stem cell therapy for autism in that there was no significant change in any tests post-treatment over pre-treatment assessments. Only 1 of the clinical trials looked at changes in immune markers in the subjects. Many of the trials established modest evidence of safety, although there were some untoward side effects such as epileptic seizures, headache, nausea and vomiting when the stem cells were administered into the spinal cord covering. Most studies had short follow-ups, varying from 6 months to 21 months. Overall, there was very little hard (scientific) evidence of stem cell "therapy's" actual effectiveness for treating autism. In fact, experts in the field have questioned the legitimacy of these trials with regards to their scientific basis, the trial design, methods of measuring the results, and their interpretation. The variability in the studies makes comparisons difficult, thus making it harder to arrive at any robust conclusions [8]. Further research is warranted before any firm conclusion about stem cell treatment in autism can be arrived at.

Lack of Regulation of Stem Cell "Therapy"

It is regrettable that the potential of stem cells has spawned a rampant stem cell industry for conditions for which no effective treatment or cure exists- such as autism - in many developed and developing countries worldwide [11], including India. Most of these take advantage of a loophole in regulations that may exist, which enables stem cells extracted from the individual's own body to escape stringent regulations that are applicable to other types of stem

cells. Thus, despite insufficient evidence of their effectiveness, stem cell 'therapies' are carried out in unlicensed clinics, sometimes under the guise of "clinical trials" and usually with exorbitant charges. In India this has given rise to a "stem cell tourism" with websites advertising cheaper stem cell therapies than in the West. One such website listed a choice of 118 centres conducting stem cell therapy for autism and other conditions, in different cities and towns of India. These are replete with exaggerated testimonials and unsubstantiated claims of "cures" and "return to normalcy" after stem cell "therapy". Anecdotal reports on social media and in newspapers further compound this impression.

Recognizing this state of affairs, the Indian Council for Medical Research (ICMR), which is the apex regulatory body for bio-medical research in India has formulated guidelines for stem cell therapy for human diseases [12]. Herein they categorically specify that **"Critical review of the studies reported so far does not support the use of stem cell therapy over and above the behavioural and supportive therapies for ASD. Recommendations (2021): Based on the review of available scientific evidence, stem cell therapy should NOT be offered as a standard or routine therapy to patients with Autism"**. Further, **"Participants in a clinical trial should not be made to pay for any expenses incurred beyond routine clinical care and which are research related including tests, investigations and any interventions (such as stem cells). This is applicable to all participants, including those in comparator/control groups. Participants in a clinical trial should be provided compensation in the event of any harm or permanent injury or death due to the use of experimental stem cell therapy."**

The ICMR has also objected to amendments proposed by the Ministry of Health and Family Welfare to the Drugs and Cosmetics Rules, 1945 on the regulation of stem cell procedures. The amendments seek to exclude minimally manipulated stem cells (stem cells that have not

undergone much processing after being removed from the body and before being transplanted again) from being defined as new drugs. Such an exclusion will mean that these cells will not need to be tested in clinical trials for efficacy and safety before they receive market approval. If passed, these amendments may legitimise the use of unproven stem cell therapies in India [13].

In conclusion, the current use of stem cells as "therapy" for autism is as of yet unverified and not recommended [12]. Further research is required to determine its safety and efficacy. Parents of individuals participating in clinical trials for the same need to be aware of the financial and ethical guidelines as formulated by the ICMR (see above). The current mainstays for managing autism are still the standard behavioural and supportive therapies. Beyond these, the question that still needs to be considered is whether autism needs to be "cured" at all or can it be considered another aspect of human diversity that needs more inclusiveness?

**Dr. Uma Ladiwala qualified with an M.D. in Pathology from the Grant Medical College, Mumbai. Some years after, she switched to a career in basic scientific research, dedicated to basic neuro-immunology research, with post-doctoral stints in Mumbai and abroad at institutes in Sweden and Canada. On her return to India in 2001, she worked at the Tata Institute of Fundamental Research (TIFR), Mumbai, researching on neural stem cells, and continued this further when she set up her own lab as Faculty at the new UM-DAE Centre of Excellence in Basic Sciences, Mumbai. She has authored and published several articles in recognised Indian and international journals and presented at a number of national and international conferences.*

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