

Here are the replies from Dr. Alok Sharma of Mumbai's NeuroGen Brain and Spine Institute to specific questions posed by the Sunday Times:

- **When did you begin stem cell therapy for autism and other neuro-developmental disorders in India? Have the Indian medical regulatory authorities approved this therapy for autism and other neuro-developmental disorders? Is your institute managed by the state or by a private company? If it is run by a private company who is doing so?**

NeuroGen Brain and Spine Institute was established as a centre of excellence for neurological disorders in December 2008. The work was initiated based on the Stem Cell Guidelines at that time which put the work we were doing with autologous minimally manipulated cells in the permissive category and this could be done with permission of the Institutional Committee for Stem Cell Research and Therapy (IC-SCRT). We have the IC-SCRT approval for this therapy for autism, cerebral palsy, intellectual disability and other conditions as well. Since, then we have treated more than 6,500 patients of incurable neurological disorders with around 50% being cases of neuro-developmental disorders and neuromuscular disorders.

We also follow the WMA Declaration Of Helsinki – Ethical Principles For Medical Research Involving Human Subjects which states *“In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.”*

Hence, we treat only incurable neurological disorders, which have no or limited treatment options.

NeuroGen Brain and Spine Institute is a private institute which is a centre of excellence for neurological disorders. We are the pioneers in the field of stem cell therapy for neurological disorders. We make use of a holistic, comprehensive approach which includes stem cell therapy and neuro-rehabilitation to treat our patients.

- **Is stem cell therapy for autism and other neuro-developmental disorders being offered in any other country in the west or the east? If so, what are the countries?**

Yes, stem cell therapy for autism and other neuro-developmental disorders is being offered in other countries throughout the world. The pioneers of this therapy are from the eastern world with the leaders being Japan, China, Korea and India. It is being offered in different countries in the continents of Europe, North and South America and Africa too but the numbers of such centers is much less than those in Asia.

- **Have clinical trials been carried out either by your team or any other team with regard to stem cell therapy for autism and other neuro-developmental disorders? If so, where**

and what are the number of cases and controls? From whom was ethics approval obtained? Were the results of the clinical trials published in any peer-reviewed journals? If so where and when? Were there any adverse events reported? If so, what were they?

The first ever proof of concept study in the world demonstrating positive outcome of stem cell therapy in autism was published in the prestigious 'Stem Cell International' journal by NeuroGen Brain and Spine Institute in 2013. We have attached the paper herewith for your reference. Following which, groups in China and USA also published their clinical results in peer reviewed journals. Recently, a clinical trial conducted by Duke University, North Carolina, USA was just completed and published. There were no adverse events reported in any of these publications. The detailed results can be obtained from the publications.

- **In India, how many children suffering from autism and other neuro-developmental disorders have been treated with stem cell therapy? What has been the success rate and what were the significant changes seen in these children?**

In India, approximately 1 in 500 children are diagnosed with autism. We have treated more than 850 patients with autism and more than 1,100 patients with other neuro-developmental disorders. Our success rate is approximately 90 percent and significant changes have been seen in these children. Our results are in our published papers.

- **How many Sri Lankan children with autism and neuro-developmental disorders have you and your team treated at your institute? What have been the follow-up and success rates? After the stem cell therapy, are other interventions for autism etc., halted immediately? Otherwise, how can the success be measured? How much does your institute charge per patient and how long does the patient have to stay in Mumbai?**

We have treated 17 patients with autism and other neuro-developmental disorders from Sri Lanka. They have shown good improvements on follow up. Patients who had undergone stem cell therapy 3-9 months back were followed up personally and clinical improvements were noticed. There was a significant change in patients' overall understanding level. Hyperactivity was reduced by 50%. Improvement was observed in speech and communication. They started using more words in their vocabulary, sensory issues like hypersensitivity towards sound and touch was reduced significantly. Behavioural issues like self-talk, stimming, laughing and crying without reason was significantly reduced. Their social interaction and eye contact had increased. They started mixing up more with their family and peers. They were more independent in carrying out their Activities of Daily Living (ADLs) like dressing up, bathing, eating, etc.

Along with stem cell therapy, we recommend neuro-rehabilitation to be done simultaneously. We can measure the effect of intervention by comparing the patients' clinical and functional presentation before and after stem cell therapy. We have observed that children who are already undergoing neuro-rehabilitation before stem cell therapy have limited improvements. However, after stem cell therapy, the improvements are accelerated and are remarkable. Changes are not only seen in clinical symptoms but are also objectively quantified as improvement in PET scan of the brain.

The cost of the treatment depends on many factors such as what type of accommodation they opt for and their socio-economic conditions etc. Some patients have also been treated at no cost.

- **How many times have you and your team visited Sri Lanka to promote stem cell therapy for autism and other neuro-developmental disorders? What are the organizations that you and your team have been liaising with in Sri Lanka? Have you done the same in other countries? If so, what are those countries and when? How many patients from foreign countries have you and your team treated?**

We have visited Sri Lanka twice. Once in November 2017 and second time in April 2018. Both the times it was at the invitation of various organizations in Sri Lanka. We do the same in several other countries of the world. We have conducted similar seminars in USA, UAE, Nigeria, South Africa, Namibia, Uganda, Kenya, Mozambique, Maldives, UAE, Vietnam, Maldives, Mauritius. Next month we have such seminars in the UK and Canada as well.

We have treated over 1,400 patients from different countries throughout the world.

- **In autism, doctors still don't know where the exact lesion is in the brain – most evidence shows changes in several areas or general changes in the brain MRI. So how would those performing stem cell therapy know what will work where?**

This was true earlier. But not anymore. It is true that the MRI scan does not show any evidence but a newer form of imaging called PET CT Scan does show. We have for the past several years been researching what the exact brain areas are in autism that are functioning less than normal. All our findings have been put together in a paper that has been accepted for publication in the World Journal of Nuclear Medicine, the title is 'The Baseline Pattern and Age-related Developmental Metabolic Changes in the Brain of Children with Autism as Measured on Positron Emission Tomography/Computed Tomography Scan'.

It is a controlled study which analyses the brain metabolism and developmental changes of brain among different age groups in autism and compares it to the healthy controls.

We observed that the autism group showed age-related linear decrease in metabolism of brain. These findings demonstrate atypical neuro-developmental trajectory of brain maturation in autism. Autism population showed the age-related decrease in SUVs uptake in the cortical region with varying uptake in all the four lobes. The brain metabolism in autism is affected across different parts of the brain with the frontal and temporal being affected more as compared to the parietal and occipital cortices.

Since this paper has been accepted for publication but not yet published we cannot send you a copy.

Stem cells create a balance in the brain where there is imbalance. Some parts of the brain are particularly affected in autism such as cerebellum and mesial temporal which includes amygdala and hippocampus (as evidenced by PET CT Scan of the brain). These areas are hypometabolic thereby leading to lack of social interaction, eye contact, emotional expression, communication,

articulation, dysarthria, fine motor activities, sensory issues, reduced tone of the body. The rest of the brain cortex is often hypermetabolic as a reaction to the low functioning of the deeper parts of the brain. This has been exclusively studied by NeuroGen Brain and Spine Institute and hence we are able to address this issue using stem cell therapy.

In addition to this, there is enough evidence available in the form of publications in peer reviewed journals which establish the mechanism by which stem cells work in autism and other neuro-developmental disorders.