CASE REPORT

Autologous Bone Marrow-derived Mononuclear Transplantation in Rett Syndrome

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ABSTRACT

Rett syndrome is a neurodevelopmental disorder that is classified as a pervasive developmental disorder. It almost exclusively affects girls leading to cortical atrophy, stereotyped hand movements, dementia and extrapyramidal dysfunction. It is characterized by normal early growth and development followed by a slowing of development, loss of purposeful use of the hands, distinctive hand movements, slowed brain and head growth, problems with walking, seizures and intellectual disability. We present a child with Rett syndrome. She underwent autologous bone marrow mononuclear cell transplantation with a mean of 12 × 10^7 mononuclear cells. Post-transplantation, the patient had no side effects and her clinical course after the transplantation was uneventful. In a period of one month, her spasticity and rigidity had reduced. The frequency of the absence seizures had also reduced significantly. The results show that the treatment was safe, effective and resulted in significant improvements.

Key words: Rett syndrome, autologous, bone marrow, mononuclear cells

Rett syndrome is a progressive neuro-development disorder, majorly affecting the females following normal psychomotor development during the 6-40 eight months of life.[1] However, it can also have its onset late in the adolescence. Characteristic features of Rett syndrome involve cognitive and functional impairment, loss of previously acquired speech, gradual loss of purposeful hand movements and development of stereotypic hand movements, gait dyspraxia, deceleration in the rate of head growth and growth failure. Seizures, abnormal breathing patterns, autonomic nervous system dysfunction, rigidity, dystonia and further development of scoliosis in later stage are also observed. The social skills of the children suffering from Rett syndrome are also impaired.[2-3] However, due to different stages and age of presentation of symptoms, Rett syndrome gets frequently misdiagnosed as a neurological illness. The mortality rate among children with Rett syndrome is found to be 1.2%/year.[4] Since, the disorder is rare, very little is known about long-term prognosis and life expectancy.

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Case Report

An 11-year-old girl child, born of a nonconsanguineous marriage, had a full term normal delivery at the hospital. At birth her weight and height were normal. She was diagnosed with Rett syndrome at the age of three years. She had no family history.

She showed normal milestones till the age of three years except speech. At about three years there was regression in her developmental milestones. She showed a history of convulsions at three years of age where in the myoclonic seizures lasted for two seconds with a frequency of recurrence after every 20 minutes. These seizures were controlled with medication and gradually reduced to once in six months and later once in a year. She also had a history of absence seizures 4-5 times a day. By the age of six years she showed physical regression. There was deterioration in walking, talking and co-ordination. She also showed characteristic stereotyped hand movements. At the age of eight she stopped walking and developed contractures. There was an increase in her involuntary movements. She had no bowel or bladder control. Thus, on the basis of clinical presentation, she was diagnosed as Rett syndrome.

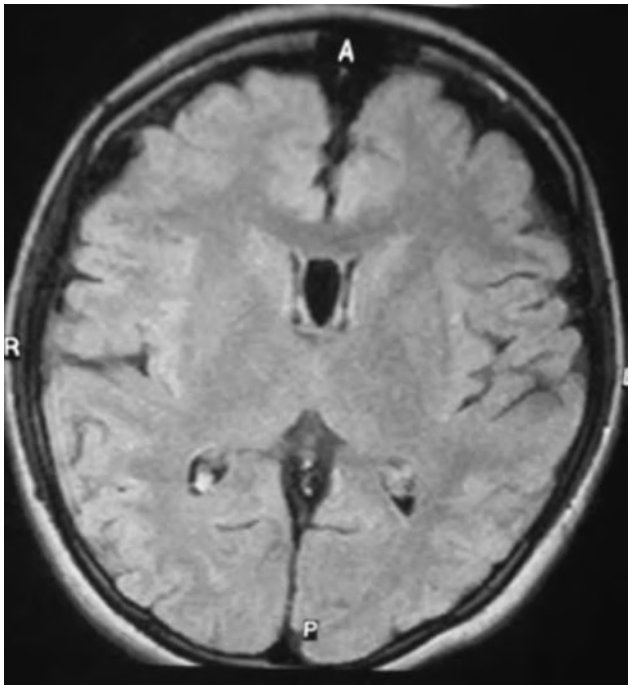

Figure 1. MRI of brain showing diffuse cerebral atrophy which was predominantly cortical.

Neurologically, she was hypertonic with cogwheel type of rigidity. She showed cognitive involvement with delayed reaction time. Her IQ test showed low IQ. Functionally, she was wheel chair bound and dependent for all the daily activities on her mother. She could walk with assistance with a Crouch Diplegic Spastic Gait. On FIM scale she scored 32. On investigation, EEG showed mildly dysrhythmic but symmetrical background activity. Her magnetic resonance imaging (MRI) brain revealed diffuse cerebral atrophy, which was predominantly cortical, suggestive of Rett syndrome (Fig. 1).

Following the observation of a neurological condition and its subsequent diagnosis as Rett syndrome, the patient had undergone various alternative therapies like neurotherapy and physiotherapy with no specific change in her condition.

Intrathecal autologous bone marrow stem cell transplantation was carried out as a neuroregenerative option in concert with neurorehabilitation. Bone marrow (100 ml) was aspirated from the iliac bone under sedation using a standard procedure. The mononuclear cells (MNCs) were separated using density gradient separation and approximately 12×10^7 MNCs were immediately injected intrathecally in L4-L5 space using an epidural set and catheter. A duly filled informed consent was obtained from the parents prior to the therapy. Routine preoperative blood tests, MRI brain, EEG were performed before the transplantation. G-CSF (150 µg) injections were administrated subcutaneously, 48 hours and 24 hours prior to the bone marrow aspiration. Following the transplantation, she underwent intensive neurorehabilitation which included physiotherapy, occupational therapy and speech therapy, as a part of the treatment program.

Discussion

The disorder was identified by Dr Andreas Rett, an Austrian physician who first described it in a journal article in 1966. Rett syndrome is characterized by developmental arrest, loss of communication, diminished play interest, deceleration of head growth from six to 18 months of age; stereotyped hand movements, severe dementia with autistic features, ataxic gait, hyperventilation and seizures from 1 to 4 years of age. Early school years are characterized by mental retardation, lesser autistic features. By 5-15 years, the child develops decreased mobility, spasticity, growth retardation and staring gaze.[5] It is an inherited X-linked neurological disorder. Genetically, Rett syndrome is caused by mutations in the gene methylcytosine binding protein 2 (MECP2) located on the long arm (q) of the X chromosome (Xq 28). This gene is responsible for synthesis of a protein called methylcytosine binding protein 2 MECP2, which is needed for brain development and is critical for nerve cell maturation. Diagnosis is still based on the clinical criteria, as only 70-80% of cases with typical Rett syndrome phenotype have mutations in the Rett syndrome gene.[6] The course of Rett syndrome, including the age of onset and the severity of symptoms, varies from child-to-child. Before the symptoms begin, however, the child generally appears to grow and develop normally, although there are often subtle abnormalities even in early infancy, such as loss of muscle tone (hypotonia), difficulty in feeding and jerkiness in limb movements. Then, gradually, mental and physical symptoms appear. As the syndrome progresses, the child loses purposeful use of her hands and the ability to speak. Other early symptoms may include problems crawling or walking and diminished eye contact.

There is no known cure for Rett syndrome. Treatments proposed are to ease the symptoms and to keep the patient functional as long as possible. The treatment requires a multidisciplinary approach, including symptomatic and supportive medical management such as hydrotherapy, speech therapy, physical, occupational therapy which can help children develop skills needed for performing self-directed activities (such as dressing, feeding, and practising arts and crafts). Physical therapy and hydrotherapy may prolong mobility. Some children may require special equipment and aids such as braces to arrest scoliosis, splints to modify hand movements, and nutritional programs to help them maintain adequate weight. Special academic, social, vocational, and support services may be required in some cases.[7] Since many potential therapies have not been successful in treating this disorder, autologous bone marrow derived MNC transplantation was carried out for the patient. These MNCs comprised of a variety of cells like hematopoietic stem cells, tissue specific progenitor cells, stromal cells and specialized blood cells in different stages of development. It is hypothesized that the bone marrow cells administered intrathecally contain endothelial precursors leading to angiogenesis which can further lead to regeneration of the nervous tissue and nerve growth factors. The G-CSF and methylprednisolone administered before and during the transplantation respectively helps in stimulation of CD34+ cells and also in their survival and multiplication.

Our case showed typical symptoms of Rett syndrome like cognitive impairment, problems with communication, stereotypic hand movements and pervasive growth failure that was followed by a normal period of development during the first few years of life. She was diagnosed on the basis of clinical presentation. Post-stem cell therapy, the patient had no side effects and her clinical course after the transplantation was uneventful. In a period of one month, her spasticity and rigidity had reduced. The frequency of the absence seizures had also reduced significantly.

We have demonstrated the possibility of use of autologous hematopoietic stem cells in the case of Rett syndrome. Further clinical trials and extensive follow-up is required to demonstrate optimal effect of the stem cells as a supportive medical assistance for Rett syndrome.

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