

# A Novel Genetic Syndrome Presenting with Developmental Delay and Microcephaly: A Case Report

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## Abstract

**Background:** The rare and unique case presentation of the patient's condition, global developmental delay, microcephaly, and the familial pattern.

**Case Presentation:** A 14-month-old female with microcephaly with symptoms of delayed speech, delayed motor milestones, and weight/growth lag. The family history of an elder sister with similar symptoms and the unaffected twin brother. Her MRI findings (simplified widening of gyri, small brain size) and the chromosomal study WES results suggest an autosomal recessive trait. Mothers do not have any history of TORCH infection prenatally or antenatally.

**Intervention & Outcome:** Detail the multidisciplinary therapeutic approach, including intrathecal stem cell therapy, BIONICA-MDI therapy, rehabilitation, and micro currents. The positive outcomes have been noticed in terms of improvements in neck holding, walking with minimal support, eye contact improvement, social interaction, social smile, and babbling.

**Conclusion:** The potential of this combined therapeutic approach of stem cell therapy, BIONICA-MDI, rehabilitation program, and micro currents can help patients to manage the symptoms of this rare genetic condition, and patients can achieve a meaningful, self-sufficient, and disease-free life. There is a need for further research into the underlying genetic mechanism.

**Keywords:** Microcephaly, BIONICA-MDI, Delayed Development, Neurological Disorders

## 1. Introduction

Microcephaly is a neurological disorder defined by an unusually tiny cerebral cortex and a head circumference that is more than two standard deviations below the population mean [1]. In primary or non-syndromic microcephaly, the distinctive small head of microcephalic individuals may be the only developmental trait. Alternatively, microcephaly; also referred to as syndromic microcephaly; may

manifest in conjunction with other comorbidities. These comorbidities, which are seen in a variety of human syndromes like primary recessive autosomal microcephaly, microcephalic osteodysplastic primordial dwarfism type II (MOPDII), and Seckel syndrome, include but are not limited to intellectual disability, epilepsy, eye abnormalities, short stature, etc. [2, 3]. When a child's head circumference (HC) is less than two standard deviations (SD) from the mean for their age and sex on the WHO growth charts, it is deemed microcephalic by the World Health Organization (WHO) [4].

Microcephaly can result from a variety of chromosomal abnormalities, including trisomies 13, 18, and 21, as well as single-gene illnesses that interfere with proper brain development. Brain development during pregnancy can be impacted by maternal illnesses such as hyperphenylalaninemia. Toxoplasma, rubella, cytomegalovirus (CMV), herpes simplex, TORCH agents and others (Zika virus, syphilis, HIV, varicella, and parvovirus B19) are major prenatal causes [5]. Pregnancy-related Zika virus infection is a known viral cause of microcephaly and severe fetal brain abnormalities [6]. Microcephaly can be caused by maternal substance abuse (alcohol, cocaine), exposure to teratogenic medications, toxins (lead, mercury), ionizing radiation, and severe starvation during pregnancy [4].

Conditions or events that result in a child's head ceasing to grow or the brain shrinking after birth, leading to a smaller-than-normal head size, are referred to as postnatal causes of microcephaly. Acquired microcephaly can result from severe brain infections in infancy or early childhood, such as meningitis, encephalitis, or other brain illnesses. Microcephaly and stunted brain development can result from neonatal physical trauma or vascular events [7]. Some genetic illnesses manifest with normal head circumference at birth but exhibit decreased brain growth later, such as Rett syndrome, Angelman syndrome, and others requiring abnormalities in genes affecting brain development after birth [8].

A primary cause of microcephaly is the loss of the neural stem cells (NSCs) essential for neurogenesis [9]. NSCs are the progenitor cells of the nervous system, and they undergo asymmetric cell division to create one self-renewing stem cell and a daughter cell fated to differentiate into neurons or glia [10].

Microcephalin (MCHP1) and aberrant spindle-like microcephaly related (MCPH5) have been the focus of most of the research. However, the recent finding of microcephaly caused by mutation of the N-myc (also MYCN) proto-oncogene, both in mice, where it was directed precisely to neural stem cells, and in the germ line in humans in Feingold syndrome, has shed new light on the role of neural stem cells in brain growth. N-myc governs brain growth not just by regulating neural stem cell proliferation, but also through retaining a neural stem cell identity at least in part via a mechanism involving global chromatin. Interestingly, along with microcephaly, mutation of N-myc also causes chromatin condensation in neural stem cells, while premature chromosomal condensation (PCC) is detected with mutation of MCHP1. The fact that 2 genes required for brain development are both essential for appropriate chromatin structure shows that the global chromatin activity state of neural stem cells is a significant element in the regulation of brain mass [11].

Rehabilitation is very important in microcephaly, because there is no cure for the small head size, but therapy can help the child reach the best possible level of function [2]. Early, consistent intervention uses brain “plasticity” in the first years of life and is linked to better developmental outcomes, even though research evidence is still limited in quality [12].

In this article, we will be discussing mesenchymal stem cells (MSCs) and BIONICA-MDI for the treatment of microcephaly. With timely intervention of MSCs, BIONICA-MDI, and rehab, there can change in the outcome.

## 2. Case presentation

A 14-month-old female presented to StemRx Biosciences Solutions Pvt Ltd, Navi Mumbai, with microcephaly, symptoms of delayed speech, delayed motor milestones, and weight/growth lag. The family history of an elder sister with similar symptoms and the unaffected twin brother.

### 2.1 Laboratory findings

Her MRI findings (simplified widening of gyri, small brain size) and the chromosomal study WES results suggest an autosomal recessive trait. The patient's mother does not have any history of TORCH infection prenatally or antenatally.

ORION's whole exome sequencing identified a probable compound heterozygous pathogenic variant alongside a variant of uncertain significance (VUS); it is recommended that these findings be interpreted in the context of clinical information for proper diagnosis and management.

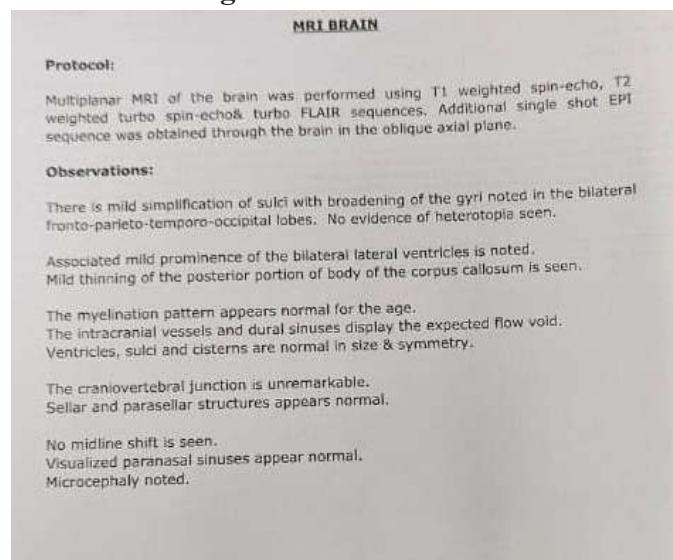
### 2.2 Treatment protocol

The patient was initiated on a regenerative therapy protocol. Detail the multidisciplinary therapeutic approach, including intrathecal stem cell therapy, 12 sessions of BOINICA-MDI therapy, and rehabilitation and micro currents.

## 3. Results

The positive outcomes have been noticed in terms of improvements in neck holding, walking with minimal support, eye contact improvement, social interaction, social smile, and babbling.

**Figure 1: MRI of brain**



**Figure 2: Mild simplification of gyri with broadening of sulci**

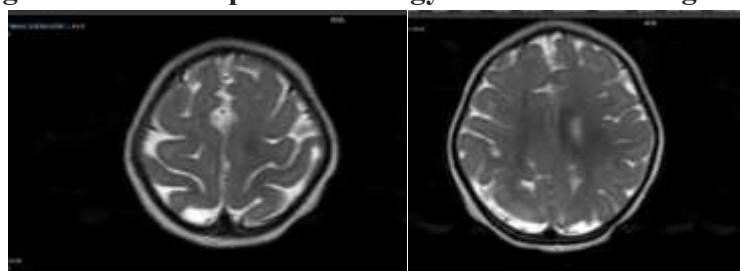


Figure 3: WES report

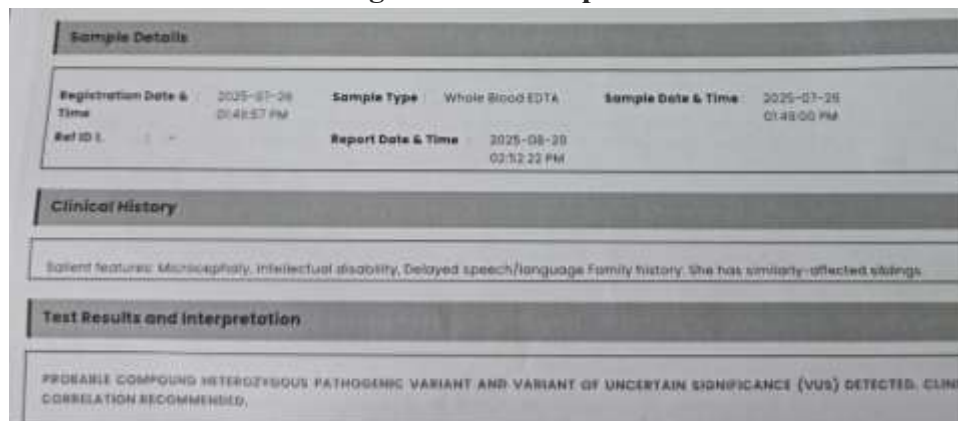
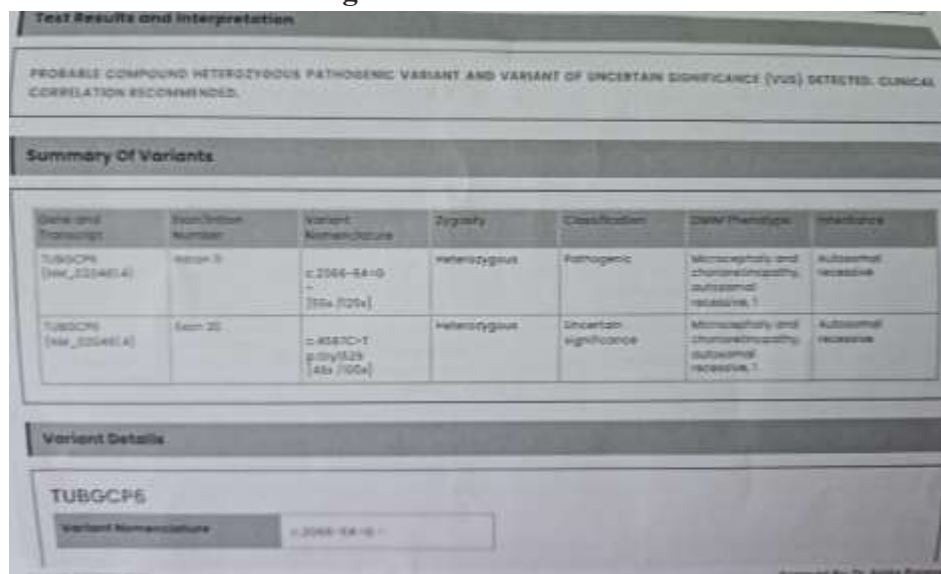


Figure 4: Variant details



#### 4. Discussion

Mild to moderate non-progressive intellectual disability, a smaller but structurally normal brain, particularly in the cerebral cortex, and a markedly smaller head circumference at birth are the hallmarks of autosomal recessive primary microcephaly (MCPH), a rare neurodevelopmental disorder. This disorder, which is more common in families with high rates of paternal consanguinity, is caused by autosomal recessive mutations affecting genes involved in neurogenic mitosis, which results in fewer neurons being created during development. MCPH is linked to at least seven distinct genetic loci, and numerous genes, including ASPM, have been found to be relevant. This makes the illness useful for comprehending both treatment strategies and the evolutionary rise in the size of the human brain [13].

An HCZ score of less than two indicates congenital microcephaly [14]. Congenital microcephaly is thought to affect 0.5% of live births in typical epidemiological settings, and the frequency of secondary microcephaly (postnatal onset) is much greater [15]. Fetal exposure to teratogens or vascular and viral problems during pregnancy are examples of environmental causes of congenital microcephaly [16, 17, 18].

Early intervention is essential during a child's vital developmental stages. For example, a study discovered that children under the age of two benefited greatly from the intervention compared to older children [19].

Developmental milestones are the most important elements for concentrating on assessment and planning, and individual aspects are crucial to the success of early intervention programs. Most children's developmental growth has been shown to follow certain patterns, and certain indicators of outcomes, including impulsive movements, have been identified [20, 21, 22]. The child with microcephaly underwent a structured rehabilitation program that included Functional Electrical Stimulation (FES) for globally weak muscles, neurodynamic techniques for neck holding and trunk control, stretching, matrix and rhythm-based training, and VIPP (very intense pulse pressure) to support home stimulation. Cognitive improvement strategies through non-invasive brain stimulation were also incorporated to enhance engagement and developmental learning.

After the intervention, the child showed partial improvement in key motor milestones, specifically partial neck holding and partial trunk control. While progress was limited, the gains indicate a positive initial response to the multidisciplinary rehabilitation approach.

A survey of the literature suggests that the mechanism of MC (microcurrent) therapy may entail the modulation of neuroinflammation, particularly through the regulation of MAPK signaling pathways. Numerous research findings indicate that MC therapy may be able to lessen the neuronal damage brought on by neurodegenerative diseases. In addition to reducing oxidative stress, apoptosis, and neuronal excitotoxicity, MC treatment successfully maintains neuronal integrity. Particularly encouraging are MC treatment's potential to stop synapse loss and its effects on synaptic degeneration [23].

The term MSG refers to a group of primary microcephalies that are known to exhibit an abnormally simple gyral layout without thickening of the cerebral cortex [24, 25, 26, 27, 28]. MSG patients frequently exhibit a number of related developmental brain abnormalities, including delayed myelination, periventricular nodular heterotopia, and corpus callosal hypogenesis and hypoplasia [29, 30, 31].

By encouraging tissue regeneration or reducing inflammation, stem cell treatment is a regenerative medicine technique that may reduce morbidity and mortality. This subject has advanced due to an increase in clinical trials examining the safety and effectiveness of stem cell treatment in pediatric illnesses. Nowadays, a variety of stem cell types and sources are used to treat juvenile illnesses. Because different stem cell sources have distinct characteristics and modes of action, stem cells can be applied in a way that is specific to the pathophysiology of the illness. The use of stem cells to treat pediatric illnesses has produced encouraging results [32].

Precision physical therapy, also known as epigenetics in physical therapy, is a developing area that studies how ubiquitous environmental influences, such as exercise, can control gene expression (the process of using the information in a gene to synthesis a functional gene product) [33].

Environmental influence implies that even if a defective gene or chromosome persists, rehabilitation can affect the extent or manner in which the gene's instructions are executed, ultimately optimizing the body's response and adaptation to the current genetic profile, resulting in improved functional outcomes and general health [34].

Since energy uptake determines glucose uptake in neurons rather than plasma glucose levels, hyperglycemia does not cause an increase in glucose uptake in neurons [35]. The connections seen in neurological patients may also be disrupted by a decrease in glucose intake.

Pulsatile insulin therapy, also known as BIONICA-MDI, consists of three hours of pulsatile intravenous insulin infusions spaced six minutes apart [36]. It aids in returning insulin levels to the physiologically appropriate range. This can happen by rhythmically delivering insulin to the portal vein and stimulating the pulsatile component of hormone release from existing  $\beta$ -cells [37, 38].

It has been shown that BIONICA-MDI therapy works well. By lowering the harm caused by excessive lipid metabolism and replenishing lost cellular energy, it prevents and reverses problems.

**Figure 5: BIONICA-MDI setup [38].**



The liver produces 43 enzymes, which are required for the generation of ATP in each organ. BIONICA-MDI is a crucial part of this treatment where pulsatile insulin increases the metabolic enzymes in glycolysis and Krebs cycle, maintains peripheral insulin receptor activity and glucose uptake, and has a stronger hypoglycaemic effect, by minimizing the harm caused by excessive lipid metabolism and replenishing depleted cellular energy, decreased OS, and inflammation. It prevents and reverses problems [38].

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