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Case Report

Clinical observations following an integrated therapeutic intervention in DiGeorge syndrome: a case report

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Abstract

Background: DiGeorge syndrome, also known as 22q11.2 deletion syndrome, is a multisystem genetic disorder associated with developmental, immunologic, endocrine, cardiac, gastrointestinal, and neuropsychiatric symptoms. Although metabolic and regenerative methods are currently being developed, management is primarily supportive and multidisciplinary.

Case Presentation: Global developmental delay, significant speech impairment, behavioral problems, anxiety, tantrums, hyperactivity, and poor social interaction were all present in an 8-year-old child with 22q11.2 deletion syndrome. Bone marrow-derived mesenchymal stromal cells, exosome-based therapy, HDAC modulating molecules (TTK, NHK477), mannitol, hyperbaric oxygen therapy, ozone, red-light therapy, microcurrent stimulation, rehabilitation, brain stimulation, neuromodulation, behavioral and occupational therapy, intonation-based intervention, and a single fecal microbiota transplantation session comprised the multimodal intervention.

Results: While in the hospital, functional communication, echolalia, hyperactivity, anxiety, frequency of tantrums, independence, awareness of the environment and safety, and social interaction all improved.

Conclusion: The results are limited to a single example and are tentative. To ascertain the effectiveness, safety, and role of specific therapy, controlled studies with standardized assessments and long-term follow-up are necessary.

Keywords: Bone marrow-derived mesenchymal stromal cells (BM-MSCs), DiGeorge Critical Region 6 (DGCR6), DiGeorge syndrome, Mitochondrial malfunction

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1. Introduction

DiGeorge syndrome, which is now recognized as part of the larger spectrum of 22q11.2 deletion syndrome, includes a variety of prenatal, immunologic, developmental, and psychiatric symptoms brought on by abnormal pharyngeal arch development. DiGeorge syndrome, which includes learning impairments, palate abnormalities, thymic hypoplasia, hypocalcemia, heart anomalies, and a significantly increased risk of schizophrenia spectrum illnesses.[1] Dr. Angelo DiGeorge first described the syndrome in 1965, and it is characterized by immunodeficiency, hypoparathyroidism, and congenital cardiac disease.[2] Complete DiGeorge syndrome, defined by the complete lack of thymic tissue and significant T-cell lymphopenia, occurs less than 1% of people with 22q11.2 deletion but is a life-threatening illness that necessitates thymus transplantation. The majority of patients have partial DiGeorge syndrome, which is characterized by varying degrees of T-cell failure and frequently improves with age due to spontaneous immunological reconstitution. Implementation of TREC-based newborn screening has transformed early detection, allowing for earlier diagnosis and intervention.[3]

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Approximately 90% of DiGeorge syndrome cases are caused by a microdeletion on the long arm of chromosome 22 at the 11.2 locus as shown in **Figure 1**. which commonly affects a 3-megabase area between low copy repeats LCR22A and LCR22D.[1]

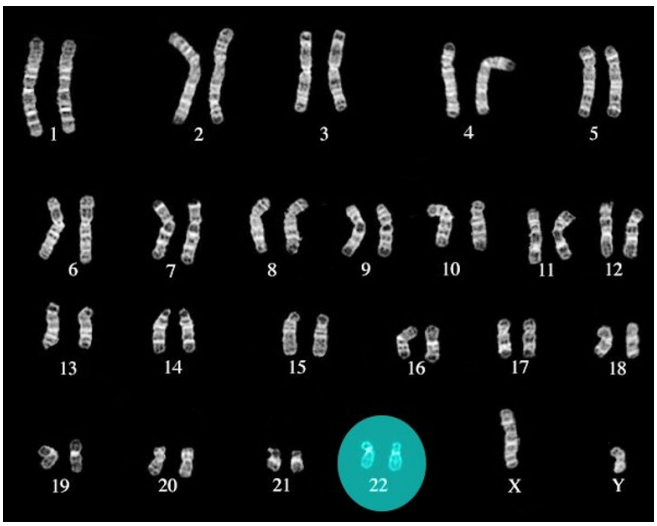

Figure 1: Digeorge syndrome Karyotype[1]

Typical treatments include developmental, speech, and occupational therapies.[4] Endocrinologists and psychiatrists follow conventional therapeutic standards to treat linked disorders such as hypocalcemia, immunological deficiencies, and psychiatric illnesses.[5,6] Antioxidants (such N-acetyl cysteine) or metabolic modulators may help restore mitochondrial deficiencies and lessen oxidative stress, according to preclinical and clinical research.[7,8]

Membrane-bound organelles called mitochondria carry out a variety of tasks necessary for the survival and proper operation of brain cells.[9] Mitochondrial malfunction may decrease the cell's ability to buffer calcium levels and increase dependency on glycolysis and ROS generation.[10,9]

The significance of the gut-brain connection in 22q11.2DS is highlighted by the substantial correlation between gastrointestinal symptoms and mental illness.[11,12] Neuropsychiatric dysfunction (disruption of the gut-brain axis), connective tissue illness (effects on dysmotility), and antibiotic use (alteration of the microbiota) are factors that may hypothetically contribute to FGIDs in 22q11.2DS.[13,12] According to the study, functional gastrointestinal diseases (FGIDs), also known as "disorders of gut-brain interaction," account for the significant burden of chronic gastrointestinal illness in 22q11.2DS.[13,12]

The gene DiGeorge Critical Region 6 (DGCR6) is likewise located on the chromosome 22q11.2 section that is commonly deleted. TBX1 is down-regulated by DGCR6, which affects neural crest migration in the pharynx.[14,15,16] Changes in the position of neural crest cells would impact the development of this area since they form the pharyngeal arch artery vasculature and the thymus capsule. Due to their respective haploinsufficiency in 22q11.2del individuals, the transcript levels of DGCR6 and its homolog, DGCR6L, should be reduced by 50%; yet, these levels are very variable in these patients.[15,16]

BM-MSCs have experimental potential for supporting thymic-stromal repair, but evidence for treating severe thymic tissue deficiency remains preclinical, mainly from animal models, and they are not an established clinical therapy.[17]

Currently, the disease-specific treatment for congenital athymic or severe DiGeorge syndrome is cultured thymic-tissue transplantation, with specialized teams providing immunological supportive care.[18]

All things considered, 22q11.2 deletion syndrome is a complicated multisystem condition that necessitates multidisciplinary care. However, new studies on mitochondrial function, epigenetic control, gut–brain interactions, and regenerative techniques may open up new possibilities for targeted treatments.

2. Case Presentation

An eight-year-old boy, the first of four sons in the family. When he was born, his mother was 26 years old; the ages of the mothers during the ensuing pregnancies were unknown. Gravida 4, para 4, four living children, and no abortions are the recorded obstetric history (GP4L4A0).

About a week after the anticipated due date, he was delivered at full term via an easy vaginal delivery. He was said to be in good health and started crying as soon as he was born. He was monitored for around 24 hours after neonatal hypoglycemia was discovered. Within 12 hours, blood glucose returned to normal, and no newborn problems were noted.

When the child was about 24 months old, the mother began to detect developmental abnormalities. The patient lacked simple words like "mamma" and "dadda," as well as meaningful vocalizations and babble. His main method of expressing his needs to his mother was by pointing at things he wanted. Although the mother stated that all developmental milestones were delayed, further information is needed to determine the precise ages at which head control, sitting, crawling, standing, walking, first words, two-word combinations, toilet training, and other adaptive skills were attained.

According to reports, when his demands are not fulfilled, he becomes irate and furious. Crying and sporadic vomiting are possible outcomes of episodes. It is necessary to conduct a comprehensive examination of the frequency, length, triggering events, and link between weeping and vomiting, including determining whether vomiting happens independently of emotional distress. The mother sought medical assessment to ascertain whether the illness was inherited or connected to environmental causes due to the severe speech and global developmental delay.

2.1. Treatment protocol

Bone marrow-derived mesenchymal stromal cells (BM-MSCs), exosome-based therapy, HDAC modulating molecules (TTK, NHK477), mannitol, hyperbaric oxygen

therapy (HBOT), ozone therapy, red-light therapy, and microcurrent stimulation were all part of the patient's multimodal treatment regimen. An intonation-based program, routine physical therapy, one fecal microbiota transplantation (FMT) session, neuromodulation therapy, behavioral therapy, and occupational therapy were all added to the regimen. The patient's clinical presentation and functional needs informed the customization of the treatment plan.

3. Results

Behavioral, linguistic, adaptive, and social domains all showed gains during the hospital stay. There was a decrease in hyperactivity, anxiety, and tantrum frequency along with an increase in independence, safety awareness, and environmental awareness. The Developmental Delay Scale score indicated mild developmental delay (95%). Functional communication increased and echolalia diminished. Additionally, the patient showed improved peer interaction, such as proper play initiation and less hostility during social activities. These are preliminary findings that call for longer-term monitoring and standardized evaluation.

4. Discussion

The present 8-year-old child's severe behavioral, social, developmental, and communicational difficulties serve as an example of the multisystemic and varied clinical manifestations of 22q11.2 deletion syndrome. The history of delayed speech, lack of early significant vocalization, delayed developmental milestones, tantrums, anxiety, and poor social interaction are all consistent with the documented neurodevelopmental and behavioral spectrum of 22q11.2 deletion syndrome. According to current clinical guidelines, developmental, speech, occupational, physical, and behavioral therapy are essential components of care and should be customized to the child's functional needs.[4]

Genes located in the deleted 22q11.2 region, such as PRODH, MRPL40, TANGO2, ZDHHC8, SLC25A1, and TXNRD2, have been connected to mitochondrial physiology. SLC25A1 encodes the mitochondrial tricarboxylate transport protein solute carrier family 25 member 1 (SLC25A1), which regulates the movement of citrate across the inner mitochondrial membrane in return for cytoplasmic malate. To sum up, SLC25A1 is an important energy regulator that affects ATP production, CAC turnover, calcium balance, and the metabolism of fatty acids and cholesterol, among other elements of cellular homeostasis. Human TXNRD2 is present in mitochondria, where it regulates ROS levels and the stability of the mitochondrial matrix. The haploinsufficiency of TXNRD2 promotes oxidative damage in the expressing neurons, impeding the formation of long-range axonal projections. Mitochondrial ribosomal protein L40 (Mrpl40) is encoded by MRPL40, a member of the polypeptide tunnel-exit of the large subunit of the mitochondrial ribosome. Finally, via regulating the synthesis of proteins that affect OXPHOS and proteins that affect calcium transfer across the mitochondrial membrane, Mrpl40 affects mitochondrial activity. PRODH encodes mitochondrial proline dehydrogenase, which catalyzes the first rate-limiting step in proline breakdown. PRODH haploinsufficiency can alter glutamate levels, affect energy metabolism by altering CAC intermediate metabolism, and cause anomalies in sensory gating. The Transport and Golgi Organization 2 Homolog (TANGO2) protein, which is encoded by TANGO2, is involved in both mitochondrial physiology and the structure and operation of the Golgi complex. Although the TANGO2 mutation is not directly linked to an increased risk of schizophrenia, it may worsen mitochondrial damage in 22q11DS by raising oxidative stress.

ZDHHC8 is involved in the generation of nitric oxide (NO), oxidative phosphorylation (OXPHOS), cholesterol transport, and synaptic function. It encodes a transmembrane zinc finger DHHC-type palmitoyl transferase 8. Through interactions with OXPHOS proteins, ZDHHC8 malfunction may negatively impact energy synthesis, NO generation, cholesterol transport, and synaptic function. Given the possible involvement of synaptic and cellular energy-related pathways linked to ZDHHC8 dysfunction in 22q11.2 deletion syndrome, microcurrent stimulation was added as an adjunctive intervention in this regard, offering low-level electrical stimulation intended to support neuromuscular and sensory stimulation and rehabilitation-related processes.[19]

Haploinsufficiency in these genes has been linked in experimental studies to problems in calcium homeostasis, increased oxidative stress, and altered energy metabolism, all of which may contribute to neuronal dysfunction.[9] A multimodal supportive and investigative procedure was used based on these possible changes in cellular metabolism, oxidative balance, and neural communication. Because exosomes can carry biologically active molecules, such as miRNAs, mRNAs, proteins, and metabolites, and may promote intercellular communication with comparatively low immunogenicity and favorable biodegradability, exosome-based therapy was included. Additionally, their potential to influence disease-associated molecular pathways provided a justification for examining their use in supporting CNS-related processes.[20] Mannitol was utilized to regulate tissue fluid balance and minimize cerebral edema or intracranial pressure when clinically warranted, whereas hyperbaric oxygen therapy (HBOT) was designed to enhance tissue oxygenation as well as metabolic and repair processes. Ozone therapy was proposed as an exploratory modality to alter redox signaling and oxidative stress pathways, whereas red-light therapy was employed as a supportive modality with effects on cellular energy metabolism, mitochondrial signaling, and tissue repair pathways. These interventions were chosen to provide complementary support for pathways that could be affected by 22q11.2 deletion-associated impairments in neuronal function, oxidative stress, calcium homeostasis, and cellular energy metabolism.[21,22]

Gastrointestinal difficulties are especially critical in this condition, as chronic gastrointestinal complaints are common in 22q11.2 deletion syndrome.[12] Patients with

22q11.2DS have more infectious, autoimmune, and allergy issues. Broader systemic problems, including as increased vascular permeability, a weakened blood-brain barrier, and epigenetic alterations produced by deletions on chromosome 22q11.2, affect various organ systems and can activate immune responses.[23] RNA sequencing of peripheral blood comparing 22q11.2DS and controls revealed altered gene expression in B cells and mast cells, which could be due to epigenetic alterations in genes beyond the 22q11.2DS region.[23,24] In view of these gastrointestinal, immune, and systemic abnormalities, fecal microbiota transplantation (FMT) was included as an investigational adjunctive intervention targeting the microbiota, gut-brain axis, with the goal of modulating intestinal microbial ecology, microbial metabolites, gut immune signaling, and downstream neurobiological pathways. The goal was to provide beneficial modification of the gut environment and its potential connections with immunological and neurological functioning in 22q11.2DS patients.[25]

Chromatin accessibility and transcription are altered by acetylation and methylation, two epigenetic modifications that affect gene expression. DNA methylation, histone modifications, chromatin remodeling, and gene-regulatory networks can all be disrupted by the loss of TBX1 and other regulatory genes in 22q11.2 deletion syndrome. Chromatin accessibility is influenced by TBX1's interaction with histone-modifying proteins, and research has shown that afflicted individuals have changed DNA-methylation signatures and histone acetylation/methylation patterns. The various neurodevelopmental, immunological, cardiac, and endocrine traits of the condition may be explained by these epigenetic changes. Nevertheless, there is currently no known treatment that may restore the deleted 22q11.2 region, and epigenetic modifications are thought of as phenotypic modifiers rather than direct replacements for the lost chromosomal material.[26,27,28] In order to modify chromatin accessibility and gene-expression pathways that may be impacted by TBX1 haploinsufficiency, HDAC-modulating molecules (TTK, NHK477) were included in this context with the goal of influencing epigenetic regulation of gene expression through histone deacetylase-related pathways.[29]

In this case, conventional rehabilitation and neuromodulation methods were combined with BM-MSCs and exosome-based therapy. Mesenchymal-cell techniques for thymic tissue regeneration in 22q11.2 deletion rats have been investigated experimentally.[17] In order to offer paracrine and immunomodulatory signaling, BM-MSCs were employed as an experimental cellular therapy. MSC-derived factors may have an impact on cellular communication, tissue repair, and inflammatory pathways. Extracellular vesicles containing proteins, lipids, and nucleic acids were used in exosome-based therapy, an experimental strategy that may have an impact on neuronal signaling, tissue repair, inflammatory reactions, and cell-to-cell communication.[30]

In order to address the neurodevelopmental symptoms of 22q11.2 deletion syndrome, neuromodulation was added. Non-invasive stimulation was used to modify neuronal excitability and activity within networks related to executive function, attention, learning, and cognitive processing; methods like transcranial alternating current stimulation (tACS) are being studied for their potential to affect neural network synchrony and neuroplasticity.[31]

Cultured thymus tissue transplantation is still a specialized disease-directed treatment for children with severe congenital athymic, but individuals with partial thymic malfunction usually need supportive care and specialized immunological monitoring.[18] The advantages discovered in this instance are therefore clinically advantageous, although they should be regarded as preliminary results from a single case. Future reviews should incorporate standardized symptom rating questionnaires, thorough genetic-report analysis, rigorous developmental and cognitive tests, longitudinal gastrointestinal and behavioral assessments, and documentation of therapeutic dosage and timing. Follow-up would help distinguish treatment-related improvements from normal developmental variation, the impacts of certain multimodal program components, and the effects of intense therapy.

The current care of 22q11.2 deletion syndrome is primarily supportive, focusing on related cardiac, endocrine, immunological, speech, neurodevelopmental, and psychiatric symptoms. Current research does not yet offer a treatment capable of repairing the underlying chromosomal loss or restoring the related epigenetic changes. Instead, clinical trials and translational pipelines are looking into tailored approaches, such as neurodevelopmental medicines like NB-001 and cell- and gene-based treatments for severe thymic and T-cell immunological deficiencies. Epigenetic medicines, such as HDAC inhibitors, are still largely experimental.

5. Conclusion

This case study reports an 8-year-old child with 22q11.2 deletion syndrome (DiGeorge syndrome) and profound verbal, developmental, behavioral, and social issues who received a multimodal therapy intervention. Hyperactivity, anxiety, tantrums, environmental and safety awareness, independence, echolalia, functional communication, and social interaction all improved during hospitalization. These clinical observations indicate that a tailored, interdisciplinary rehabilitation approach can result in functional improvements in children with complicated neurodevelopmental symptoms of 22q11.2 deletion syndrome. However, the relevance of each component of the intervention cannot be assessed from a single case, and the findings should not be construed as proof that the genetic deletion or its underlying epigenetic, mitochondrial, or gut-brain problems were resolved. More genetic characterization, standardized symptom-scale assessment, objective pre- and post-treatment measurements, and long-term follow-up are needed to determine the clinical importance of these alterations. Further research is needed to determine the safety, efficacy, and appropriate clinical function of these multimodal therapies in 22q11.2 deletion syndrome.

6. Source of Funding

None.

7. Conflict of Interest

None.

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