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Exploring Suspected Pathogenicity of SETD5 Gene and Assessing the Impact of Speech and Physical Therapy Interventions: A Case Study Analysis with a Goal Attainment Scale Approach

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Abstract

Introduction

Global developmental delay (GDD) is a heterogeneous condition characterized by delays in reaching developmental milestones during early childhood. Recent advancements in genetic research have underlined the role of genetic mutations in contributing to various neurodevelopmental disorders, including developmental delays (DD). One particular gene of interest, SETD5, has been associated with a distinct manifestation of developmental delay.

Case description

Through a case study approach, this study investigates the suspected pathogenicity of SETD5 gene mutations in a child who is 2 years and 5 months old and assesses the effectiveness of speech therapy and physical therapy interventions in a child with these mutations using the Goal Attainment Scale (GAS). Comprehensive clinical and developmental assessments such as Magnetic Resonance Imaging, Diffusion-Weighted Imaging, Magnetic Resonance Angiography, Whole exome sequencing (WES), Copy number analysis, Speech therapy assessment, and Physical therapy assessment were performed. Pre-intervention assessments revealed significant speech and motor delays. Post-Intervention GAS Scores revealed that the child displayed an average change of 32.8 and 32 in the areas of speech therapy and physical therapy, respectively. These scores signify a positive shift in outcomes for the broader objectives within speech therapy and physical therapy.

Conclusions

The findings of this study suggest that early diagnosis and interventions offer the potential in addressing speech and motor challenges linked to SETD5-related developmental disorders, improving the quality of life for those affected and their families.

Keywords: *Developmental delay, Global Developmental Delay, SETD5 gene mutation, Genetic counseling, Neurodevelopmental disorders, Speech therapy, Physical therapy, Goal Attainment Scale*

Introduction

Global developmental delay (GDD) refers to the delay in two or more developmental domains of gross motor/fine motor, cognitive, speech/language, and personal/social, activities of daily living in young children less than 5 years of age (Majnemer & Shevell, 1995; Shevell, Ashwal, & Donley, et al. 2003; Gupta & Kabra, 2014). GDD Diagnosis is guided by the Diagnostic and Statistical Manual for Mental Disorders (DSM-5-TR). It is seen as a temporary diagnosis for children who are unable to undergo standardized IQ evaluation (American Psychiatric Association, 2013). Sometimes the terms 'developmental delay' and 'global developmental delay' are used interchangeably. There are some children diagnosed before their first birthday, while others are diagnosed when compared to other children of the same age. When children have delays, they may show a variety of symptoms based on gene mutations and have a diverse prognosis. Research indicates that speech and language delays are frequently associated with challenges in reading, writing, attention, and socialization. Hence, identifying the etiology is essential not only for managing, prognosticating, and allaying parents' anxiety but also for providing genetic counseling and prenatal diagnosis in subsequent pregnancies. (Gupta & Kabra, 2014).

Gene mutations can have various effects on developmental delay, depending on the specific gene involved, the nature of the mutation, and how it impacts the normal functioning of the gene. The SETD5 gene, encoding a histone methyltransferase, has emerged as a critical player in neurodevelopmental disorders. Mutations in SETD5 have been linked to a specific subtype of developmental delay characterized by intellectual disabilities, speech and language deficits, and motor impairments. SETD5 encodes a protein with histone methyltransferase activity, suggesting a role in chromatin remodeling and gene expression regulation. Mutations in SETD5 alter its function, leading to disruptions in epigenetic mechanisms that impact neurodevelopment. Various types of mutations, including missense, nonsense, and frameshift mutations, have been reported in individuals with developmental delays. These mutations are typically de novo, arising spontaneously in affected individuals. SETD5-related disorders are relatively rare, and researchers are still working to fully understand the precise role of SETD5 in normal development and its contributions to various medical conditions.

The diagnosis of Global Developmental Delay involves a range of tests, each serving distinct purposes. These tests encompass 1) Metabolic and Biochemical Investigations delve into metabolic and biochemical aspects. Genetic, molecular, and metabolic tests, conducted using blood or urine samples, can identify hereditary causes of global developmental delay (as per the American Academy of Neurology, 2014). These tests also analyze body chemistry abnormalities contributing to developmental delays. Furthermore, tests like lead screening can identify toxic elements in the environment, such as lead, which can harm the nervous system and lead to cognitive deficits. 2) Neuroimaging methods like CT scans and MRI are employed to evaluate potential damage to the central nervous system and brain. These detailed images aid in understanding certain cases of Global Developmental Delay. MRI provides more intricate images, while CT scans are quicker and more cost-effective for patients. 3) Clinical Assessment by an Interdisciplinary Team: Clinical assessment involves a comprehensive evaluation by a team of interdisciplinary professionals such as speech therapy, occupational therapy, behavioral health, and early intervention. This assessment serves multiple purposes, including confirming and categorizing the severity of Developmental Delay, identifying potential underlying causes, proposing suitable treatment plans, offering family counseling, and managing associated medical and behavioral issues.

Case Description

This is a retrospective case study analysis of a child suspected to carry pathogenic SETD5 gene mutations. This study aims to investigate the suspected pathogenicity of SETD5 and evaluate the effectiveness of speech therapy and physical therapy interventions in addressing the associated developmental challenges. The subject of this case study is a 2-year 5-month-old boy residing with his parents in Shanghai. Comprehensive genetic testing, clinical assessments, and developmental evaluations were conducted to confirm the presence of SETD5 mutations and characterize the phenotype. Accompanied by his mother and caregiver, the child's parents sought various assessments due to concerns about delayed play, language, communication, and gross and fine motor skills. In April 2022 (at the age of 1 year 4 months), the parents observed reduced eye contact and physical/speech developmental lag, leading them to consult a children's Medical Centre where a doctor diagnosed them with a developmental delay and recommended speech and physical therapy assessments. Medical history reveals, the mother experienced good health except for gestational diabetes and cholestasis during pregnancy, which were resolved with medication. The child was born full-term via C-Section with no notable complications. There were no apparent issues during the postnatal period, and the child was reported to be in good health. The child's medical history is unremarkable, and there is no family history of speech or language disorders. The child's hearing and vision has been tested and the results were within normal limits.

1. Assessment measures

During the initial therapy consultation, a resident physician conducted a comprehensive general physical examination to assess for potential dysmorphology. This examination encompassed evaluating the growth curve, which involves assessing factors such as weight, height, and head circumference. Subsequently, based on the findings of the physical examination, discipline-specific assessments were recommended.

a) Developmental assessment

The "Gesell Developmental Schedules: Birth to Three Years" is a comprehensive assessment tool designed to evaluate the developmental progress of children from birth up to three years of age (Gesell, 1925, 1940, 1964; Ames, Gillespie, Haines, & Ilg, 1979, 2011). This assessment covers a range of developmental domains, including motor skills (both gross and fine), language development, personal-social skills, and adaptive behavior. The results of the Gesell assessment, carried out in June 2022, revealed a developmental age of 12 months for gross motor skills, 8 months for speech skills, and 11 months for socio-emotional response skills.

b) Speech therapy Assessment

The assessment commenced with a thorough case history review. This involved gathering comprehensive family history, encompassing previous investigations, family background information, maternal history, birth history, and postnatal history. The developmental milestones achieved by the child and the age at which the specific issue arose were carefully examined and recorded for documentation purposes. The Rossetti Infant-Toddler Rating Scale ((Rosetti, 2006) was administered to determine a child's communication development compared to children of his age. It is a standardized assessment tool designed to evaluate the communication and language skills of infants and toddlers from birth to 36 months. The scale provides a comprehensive framework for observing and analyzing various aspects in six areas including Interaction-Attachment skills, Pragmatic skills, Gesture skills, play skills, Language comprehension skills, and Language expression skills, helping professionals identify potential areas of concern and track developmental progress. On June 27, 2022, the child has undergone a detailed speech therapy assessment to assess his speech, language, and early communication skills. The child demonstrated

mild delays in his interaction; social skills; gestures; play, and language comprehension as evidenced by his limited ability to reciprocate with adults; and his limited ability to imitate the actions/sounds and sound combinations during play. He also exhibited moderate delays in his language expression as evidenced by his limited ability to vocalize.

c) Physical therapy assessment

Griffiths Mental Development Scales- Chinese (GDS-C) was adapted to assess the development of a child from 0 to 8 years across six separate subscales: Locomotor (A), Personal-social (B), Language (C), Eye-hand co-ordination (D), Performance (E), and Practical Reasoning (Wong, Challis, & Tso et, al, 2014, 2018; Luiz, Barnard, & Knoesen et al., 2006). Physical therapy assessment was carried out for Subscale A (locomotor) on July 4, 2022, to assess the gross motor skills. A percentile range of 10%-12.5% on the Griffiths Mental Development Scale-C signifies that the child's performance is positioned at the lower spectrum of the distribution, indicating developmental abilities (equivalent to 12 months old) that are below those of the majority of children within the normative sample.

d) Swallowing Assessment and Meal Time Management

The child was brought in for evaluation on 8 March 2023 due to concerns about his occasional choking when eating large foods and drinking. The results revealed that the child mainly uses an immature chewing action (moving the jaw up and down) to break down the food in its mouth and did not exhibit the diagonal rotational chewing action (jaw moving in a way that combines both lateral & rotational motions simultaneously) expected at his age.

e) Clinical investigation (Neuroimaging & genetic test)

The child presented with a history of feet dragging, particularly noticeable during ambulation, which has been observed for 2 weeks in the middle of the rehabilitation treatment process (i.e., Speech therapy & physiotherapy). The child's presentation of feet dragging, in conjunction with clinical and examination findings, raises the suspicion of a neurological issue. Hence, further referral and investigation were warranted to determine the precise etiology of these symptoms. A combination of advanced imaging techniques such as Head MRI (Magnetic Resonance Imaging +DWI (Diffusion-Weighted Imaging) +MRA3.0 (Magnetic Resonance Angiography) were performed to obtain detailed structural images of the brain using Head MRI, assess water diffusion patterns within brain tissues using DWI, and visualizing blood vessels in the brain using MRA. It provides valuable insights into the brain's structure, function, and blood supply, aiding in diagnosis and treatment planning. The radiological findings indicated asymmetric bilateral ventricles with slightly high signal intensity in small patches near the posterior horn of both ventricles, suggesting incomplete myelination. Brain MRA shows a closed pattern of WILLS loop, with a clear display of bilateral internal carotid arteries, vertebral arteries, and basilar arteries. ACA (Anterior Cerebral Artery), MCA (Middle Cerebral Artery), PCA (Posterior Cerebral Artery), and their branch blood vessels are visible, and there are no significant abnormal changes in their shape, size, and distribution.

Whole exome sequencing (WES) and copy number analysis are used to study genetic variations and alterations within an individual's DNA. The results concluded (Table 1) that variations were detected that might be associated with the clinical phenotypes

Table 1: Results of the Whole exome sequencing (WES) and copy number analysis

Gene	Transcription reference book	Genetic pattern	Nucleotide/amino acid changes	Zygotic state	Mother	Variant classification
SETD5	NM_001080517.3	AD	c.1043G>A/ p.ARG348Gln	Heterozygous	Normal	Suspected to be pathogenic

AD- Autosomal Dominant

Sanger verification of NM_001080517.3: c.1043G>A mutation was recommended for the child's father to identify the source of the mutation. Sanger sequencing is considered a gold standard for confirming genetic variants due to its accuracy and reliability. The results are displayed in Table 2.

Table 2: Results of the Sanger sequencing analysis

Gene	Transcription reference book	Genetic pattern	Nucleotide/amino acid changes	Zygotic state	Mother	Variant classification	OMIM related disease
TBX2	NM_005994.3	AD	c.1550G>A/ pGly517Asp	Heterozygous	Normal	Clinical significance unknown	Spinal abnormalities, variable endocrines, and Tcell dysfunction
CHD5	NM_015557.3	AD	c.*4711G>T/ p.Ala157Ser*	Heterozygous	Heterozygous		Neurodevelopmental syndromes
FOXC1	NM_001453.2	1.AD 2.AD	c.871G>A/ p.Ala291Thr	Heterozygous	Heterozygous		Subtypes of anterior segment hypoplasia 3; subtypes Axenfeld-Rieger syndrome subtype 3

AD- *Autosomal Dominant*

2. Therapeutic Intervention

The treatment foundation was meant to target the cause of the developmental delay. Since the child is experiencing a delay in gross motor and fine motor skills, it is recommended for physical therapy interventions, and the delay in speech-language skills is recommended for speech therapy.

a) Pretherapy intervention

The speech therapy intervention aimed to improve early communication skills, pre-verbal skills, communicative functions, play skills, and expressive and receptive language skills, while the physical therapy intervention targeted motor coordination and gross motor skills to improve motor coordination, balance, and strength. The child received tailored speech therapy and physical therapy interventions over 12 months. Pre- and post-intervention assessments were conducted using standardized developmental and functional scales such as GAS (Goal attainment scale, Turner-Stokes, 2009). GAS allows professionals to

set specific, measurable achievable, relevant, and time-bound (SMART) goals tailored to each client's unique needs.

b) Post therapy

Pre-intervention assessments revealed significant speech and motor delays. Following speech therapy, the child exhibited notable improvements in pre-verbal skills, communication skills, receptive language, and expressive language. Physical therapy interventions resulted in enhanced gross and fine motor skills, with the child demonstrating increased coordination and motor control and enhanced fine motor precision. As the therapy progresses, periodically (one episode of care lasts 3 months/12 weeks) assessed the child's performance on each goal using the goal attainment scale.

Table 1 and 2 summarizes the GAS scores for each participant at baseline (pre-intervention) and post-intervention assessments. The scores range from -2 (much less than expected Outcome) to 0 (expected outcome) to +2 (much more than expected outcome). Negative scores indicate that the outcome is much less than expected, while positive scores reflect outcomes that surpass expectations. The composite GAS (the sum of the attainment levels x the relative weights for each goal) is converted into a standardized measurement, represented as a T score with an average of 50 and a standard deviation of 10.

Table 3: Goal Attainment Scale-T (GAST) Scores- Speech therapy

Episodes	Baseline	Post-intervention	Change	Standard deviation	Interpretation
Episode 1	33.7	60.8	27.1	10	Positive change
Episode 2	35.5	68.1	32.6	10	Positive change
Episode 3	31.9	62.1	30.2	10	Positive change
Episode 4	34.5	75.8	41.3	10	Positive change
Average	33.9	66.7	32.8	10	Positive change

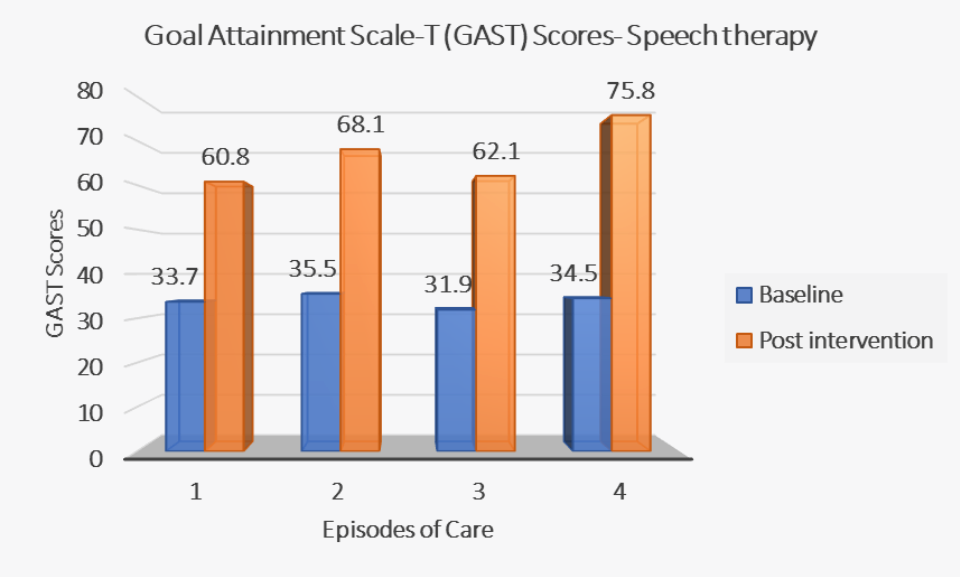


Figure 1: Pre and post-speech therapy Goal Attainment Scale-T (GAST) Scores

Table 4: Goal Attainment Scale-T (GAST) Scores- Physical therapy

Episodes	Baseline	Post-intervention	Change	Standard deviation	Interpretation
Episode 1	31.7	61.5	29.8	10	Positive change
Episode 2	32.0	60.1	28.1	10	Positive change
Episode 3	31.9	65.7	33.8	10	Positive change
Episode 4	33.5	69.8	36.3	10	Positive change
Average	32.27	64.27	32	10	Positive change

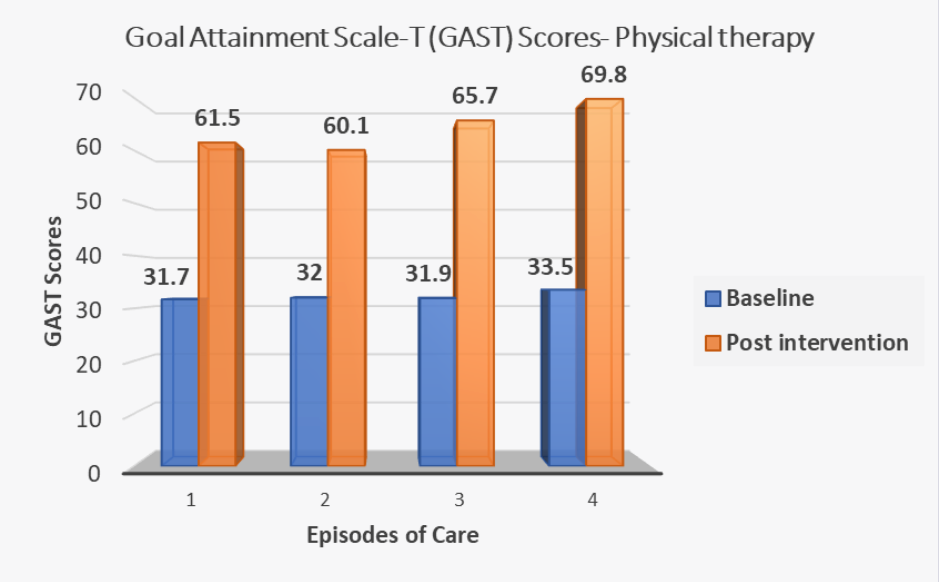
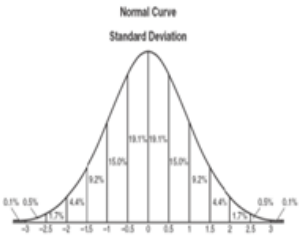


Figure 2: Pre and post-physical therapy Goal Attainment Scale-T (GAST) Scores

The overall GAS scores for the child were calculated by summing up the scores across all the goals. GAST/Gas T score is a measure of change. The GAS T scale has a mean of 50 and a standard deviation of 10. Positive scores indicate progress beyond the baseline (i.e., >50 shows positive change and a change shows clinical outcome), while negative scores might indicate less than expected or limited progress.



Gas Score Formula:

$$\text{Overall GAS} = 50 + \frac{10\,\Sigma(w_i x_i)}{[(1-\rho)\,\Sigma w_i^2 + \rho(\Sigma(w_i)^2]^{1/2}}$$

Post-Intervention GAS Scores revealed that, after undergoing 12 months of therapeutic interventions, the child displayed an average change of 32.8 and 32 in the realm of speech therapy and physical therapy, respectively. These scores signify a positive shift in outcomes for the broader objectives within speech therapy and physical therapy. In terms of speech therapy advancements, the child consistently formulates 3–4-word phrases adeptly follow 2-step instructions, and confidently engages in asking and responding to questions at the level of Blank's questions I-II. Moreover, the child demonstrates proficiency in parallel

play, and multi-step pretend play, and effectively addresses basic social inquiries. Regarding physical therapy progress, the child has accomplished the ability to independently navigate a 3-story obstacle pole, successfully ascend and descend stairs without assistance, stand unaided on one leg for 1-2 seconds, independently execute a jump from a 10cm step (with a success rate exceeding 50%), independently perform high kneeling-half kneeling-standing transfers on both sides and engage in two-footed hopping independently, without requiring assistance. Additionally, the child has attained the skill of independently using a spoon to pick up and consume food.

Discussion

A comprehensive clinical evaluation remains the central aspect for planning investigations in young children who present with Global Developmental Delay (GDD), as highlighted by prior research (McDonald et al., 2006; Silove et al., 2013; O'Byrne et al., 2016). This study explored the genetic basis and the clinical Implications of developmental Delay in Children with SETD5 Mutations. An in-depth assessment of the child's developmental status across various domains (gross motor, fine motor, language, socioemotional, and cognitive skills) using a recognized tool for normative comparison should be conducted. This study demonstrated a positive and expected therapy outcome over one year in a child with mild developmental delay. The study's findings also support the idea that SETD5 gene mutations contribute to a distinct neurodevelopmental pattern characterized by speech and language deficits, as well as impairments in gross and fine motor skills. Additionally, the study results emphasize the positive impact of targeted speech therapy and physical interventions in addressing specific developmental challenges linked to SETD5-related disorders. Thus, clinicians should consider investigating various levels of developmental delay, including persistent mild GDD, due to the diverse phenotypic presentations of genetic and metabolic conditions. The Goal Attainment Scale (GAS) reflects personalized intervention goals, offering insight into therapy effectiveness. Positive changes observed demonstrate the potential benefits of the interventions. GAS scores complement quantitative assessments by capturing meaningful goal achievement for participants and families.

Early evaluation is crucial for children with GDD, as some may eventually experience intellectual disabilities. In some instances, a lack of adequate individual attention for children with GDD leads to deficits in motor, language, social, and cognitive skills (Perna & Loughan, 2013). Placing such children in supportive environments can improve these skills before starting school. Family support is essential for aiding these children in daily activities. Each child with GDD, irrespective of the cause, should be treated as an individual, considering their personal needs for maintaining a normal life. In conclusion, SETD5 mutations have emerged as a significant genetic contributor to developmental delay. An enhanced understanding of the genetic and clinical aspects of SETD5-related developmental delay holds promise for better diagnostic precision, prognostication, and therapies, ultimately enhancing the quality of life for affected individuals and their families.

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