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Case Report

Management of autism and attention-deficit hyperactivity disorder in Dup15q syndrome

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ABSTRACT

Dup15q syndrome is an uncommon neurogenetic disorder caused by duplications of chromosome 15q11.2-13.1, typically through idic (15) or interstitial duplications. Its prevalence is about 1 in 5,000 births and is characterised by hypotonia, developmental delays, intellectual disability, autism, and seizures, with greater severity in maternally derived duplications. Symptoms overlap with related conditions such as Prader-Willi and Angelman syndromes. Early detection and intervention, supported by a robust database, will improve quality of life. An 11-year-old girl with Dup15q syndrome was referred for psychiatric evaluation due to her emotional and behavioral issues at school. She had a history of developmental delays and persistent autistic traits. Her parents noted early morning awakenings and negative self-talk. At the time of evaluation, she was receiving psychotropic and antiepileptic medications. The review found her restless and tense, with limited insight. To ensure her safety, the school provided one-on-one support during medication adjustments, and she showed some improvement in the following weeks. However, she still faced challenges with sensory dysregulation and emotional reactions. Dup15q syndrome is a complex neurogenetic disorder that requires early detection and intervention for optimal outcomes with genetic testing and personalized care strategies. Addressing the behavioral, social, and sensory challenges associated with the condition is essential, as these difficulties will intensify with age. Ongoing research and the development of support networks are vital to enhancing the quality of life for individuals with Dup15q syndrome and their families.

Keywords: Dup15q, Chromosome 15q11.2-13.1, Prader-Willi, Angelman syndromes, Case Report

INTRODUCTION

Chromosome 15q11.2-13.1 duplication syndrome, commonly referred to as dup15q syndrome, is a rare genetic disorder caused by the duplication of a specific segment on the long arm of chromosome 15. This duplication usually happens in one of two ways: either as an extra isodicentric 15 chromosome (known as idic(15)) or as an interstitial duplication (termed int dup (15)). This area of the chromosome is significant because it also plays a role in Prader-Willi syndrome and Angelman syndrome, which are related genetic conditions.[1] Dup15q occurs in about 1 in 5,000 births, making it a relatively common cytogenetic anomaly.[1] Individuals with dup15q syndrome often experience a range of symptoms, including low muscle tone (hypotonia), delays in gross and fine motor skills, varying levels of intellectual disability (ID), autism spectrum disorder (ASD), and seizures, such as infantile spasms. The severity and combination of these symptoms can vary significantly from person to person. This variability is influenced by whether the duplication is inherited from the mother or the father and by the number

of copies of the critical region on chromosome 15.[1] Those with maternally inherited duplications typically experience more severe symptoms. Common challenges include developmental delays, communication issues, and epilepsy, along with distinctive facial features that may go unnoticed in infancy. There is also a risk of psychiatric problems and sudden unexpected death in epilepsy (SUDEP).[1]

Differentiating between conditions that overlap with dup15q syndrome is essential for accurate diagnosis, with genetic testing being the most crucial factor. Paternal interstitial duplications of 15q11.2-q13.1 can present unique symptoms such as sleep disturbances and traits associated with autism. In contrast, Prader-Willi syndrome results from the loss of the paternal 15q11.2-q13.1 region. It is characterized by hypogonadism, overeating (hyperphagia) leading to obesity, obsessive-compulsive behaviors, and better verbal skills. At the same time, Angelman syndrome is caused by the absence of the maternal UBE3A gene, which leads to limited communication, seizures, ataxia, and a happy or excitable disposition. Deletions in 15q11.2 or 15q13.3 result in distinct neurobehavioral symptoms, with the former linked to language and cognitive delays. Lastly, duplications in these regions may cause developmental delays and autism, but are considered mainly variants of uncertain significance.[2]

Children with Dup15q frequently face behavioral and social communication challenges, with many meeting the criteria for autism spectrum disorder (ASD). Issues like hyperactivity, anxiety, and frustration may lead to tantrums. It's particularly associated with ASD, being identified in approximately 1 in 508 patients referred for chromosomal microarray analysis due to developmental issues.[1] In specific autism cohorts, the prevalence ranges from 1 in 253 to 1 in 522, while among individuals with intellectual disabilities, it's estimated at 1 in 584.[1] Research indicates this social interaction challenges can worsen as children grow older. Many also experience sensory processing disorders, attention deficits, and heightened anxiety, highlighting the need for further research in the Dup15q community.[2]

Dup15q syndrome is a complex genetic disorder with variability in symptom severity, often associated with parental inheritance and specific duplication characteristics, emphasizes the need for personalized assessments and interventions. Children with Dup15q frequently face significant behavioral and social challenges, which necessitate support and research. Greater attention and resources are essential for understanding and improving the lives of those affected by Dup15q syndrome.

CASE REPORT

An 11-year-old girl has been referred for evaluation due to increasing problems with aggressive and self-injurious behaviors at school. She has a developmental background characterized by Dup15q syndrome, global developmental delay, autistic traits, and disruptive mood dysregulation. The school team reported troubling behaviors, including restlessness and severe tantrums triggered by denied requests, transitions, or unmet expectations. Her parents noted that she often makes negative self-statements and experiences heightened irritability in the evenings, along with early-morning waking and difficulty adapting to routine changes. Despite multiple medication trials involving selective serotonin reuptake inhibitors (SSRIs), antipsychotics, mood stabilizers, and alpha-agonists, her response has been inconsistent.

In recent months, both her family and school observed a worsening in her symptoms, marked by more intense and prolonged aggressive outbursts, alongside incidents of biting, kicking, spitting, and attempting to choke herself. These episodes often felt unintentional, arising during overwhelming emotional states. Over two days, she required five physical restraints due to safety concerns, and in some situations, parental intervention or emergency medical evaluations were needed. She consistently struggled with transitions, especially when anticipating preferred activities, and became easily overstimulated in structured classroom settings.

During the mental status exam, the girl appeared healthy but was restless and sometimes irritable. She had a tense posture and needed frequent redirection. Her speech was short, occasionally using scripted phrases and very literal language. Her emotional responsiveness was limited and often reactive to her surroundings. Her thought processes were transparent but rigid, showing little flexibility. She was aware of who she was and where she was, but had difficulty focusing due to hyperarousal. Insight into her behavior was limited; she didn't fully appreciate the severity of her actions, though she expressed guilt and negative self-talk. Her judgment appeared impaired during dysregulation but was assessed as fair at other times.

Her current medication plan consists of Prozac 20 mg, Abilify 10 mg, Trileptal 600 mg, and a scheduled Lupron depot injection. Previous medications included Intuniv, Atenolol, Propranolol, Sertraline, and Escitalopram. Due to her recent severe episodes, her school program was temporarily modified to an environment with one-to-one supervision while medication adjustments were assessed. Moving forward, recommendations included continuation of mood-stabilizing medications, possible dose adjustments, implementation of structured behavioral strategies, and additional support for smoother transitions. Safety planning was a priority for both the family and the school team.

In the following weeks, the girl showed partial but meaningful improvement, with fewer prolonged episodes and faster recovery. Her sleep pattern became steadier, evening irritability lessened, and she handled minor schedule changes better. However, significant challenges

remained, including sensory dysregulation, difficulty with emotional regulation, and struggles with unexpected demands. These ongoing symptoms aligned with the inherent behavioral characteristics associated with Dup15q syndrome, indicating that her mood dysregulation and sensory sensitivities were fundamentally neurodevelopmental in nature. This situation calls for ongoing interventions, including behavioral therapy, fine-tuning her medication, and maintaining a structured support system both at school and at home.

DISCUSSION

Chromosome 15q11.2-13.1 is a rare genetic disorder caused by duplication of the 15q11.2-13.1 region.[1] The portion involves a small area on the long arm (q) at 15q11.2-13.1. This condition occurs when this extra copy is inherited from the mother's side due to genomic imprinting, a phenomenon in which specific genes are active only on the maternal chromosome. Usually, an individual inherits one copy of chromosome 15 from each parent. However, in individuals with dup15q syndrome, there are additional copies of the genes in the long arm (q) region, disrupting normal development and leading to the features of the disorder. These duplications most commonly occur in one of two forms: an extra isodicentric 15 chromosome (idic (15)) or an interstitial duplication 15 chromosome (int dup (15)).[1]

In the general population, the prevalence of dup15q may reach 1 in 5000. This chromosomal anomaly is among the most prevalent in individuals with ASD. For patients who undergo clinical chromosomal microarray analysis (CMA) due to developmental issues (such as developmental delay, intellectual disability, or ASD) or multiple congenital anomalies, the prevalence of dup15q is around 1 in 508. Within cohorts of ASD, the prevalence ranges from 1 in 253 to 1 in 522. In cohorts with intellectual disabilities, the prevalence is about 1 in 584.[1]

Chromosome 15 is classified as an acrocentric chromosome and is characterized by the presence of low-copy repeats (LCRs). These LCRs are found on the proximal long arm of chromosome 15 (15q11.2q13), which contributes to cytogenetic irregularities such as deletions and duplications. The suspected mechanism underlying these abnormalities is non-allelic homologous recombination (NAHR) at specific breakpoints (designated BP1-BP5) during meiosis I.[11]

Recent studies have identified patients with duplications in a specific region of chromosome 15 (15q11.2-q13) that are influenced by which parent passed the duplication on. When these duplications come from the mother, they are often associated with autism and varying levels of developmental delays. In contrast, there have been only a handful of cases where the duplication was inherited from the father, and these individuals generally show little to no symptoms, such as speech delays or behavioral issues.[9]

Research has shown that individuals with ASD may have lower levels of serotonin (5-hydroxytryptamine, or 5-HT) and reduced volume of the dorsal raphe nucleus (DRN), a brain area rich in serotonin-producing neurons that project to the cortical forebrain. Studies suggest that during development, patients with ASD experience decreased serotonin production in their central nervous system, which indicates a state of low serotonin activity. Additionally, this serotonin system appears to affect cognitive function in people with ASD, leading to behavioral issues that stem from disrupted neural networks. However, there still isn't strong direct evidence to fully support this idea.[10]

Three distinct neurodevelopmental disorders arise primarily from deletions or duplications that occur at the 15q11-q13 locus: Prader-Willi syndrome (PWS), Angelman syndrome (AS), and 15q11-q13 duplication syndrome. 3 Pis caused by the loss of the paternally inherited 15q11.2-q13.1 region. Individuals with PWS have a milder cognitive impairment and have key distinguishing features such as hyperphagia leading to obesity, hypogonadism and are typically more verbal, distinguishing them from those with dup15q syndrome.[1] AS is caused by the lack of UBE3A gene expression from the maternally inherited chromosome 15 due to various 15q11-q13 abnormalities.[4] Individuals with AS have a happy or excitable disposition, distinguishing it from Dup15q syndrome.[1]

Prader-Willi syndrome (PWS) is a neurodevelopmental condition caused by the loss-of-function of genes on the 15q11-q13 region inherited from the father. It is marked by significant muscle weakness (hypotonia), challenges with feeding, reduced sexual development (hypogonadism), smaller-than-average hands and feet, delays in development, various behavioral issues and underdeveloped genitals. Notably, children with PWS who are between 2 and 4 years old may experience an overwhelming craving for food, leading to severe obesity if their diet is not closely monitored. Approximately 70% of individuals with PWS have a deletion in the paternal 15q11-q13 region, around 25% exhibit uniparental maternal disomy (UPD) of chromosome 15, and 2% to 5% have imprinting-related issues.[5]

Angelman syndrome (AS) is a genetic disorder that affects brain development and is linked to changes in a specific region of chromosome 15 (15q11-q13), which is inherited from the mother. Most cases (about 70% to 75%) are caused by a new deletion in this part of the chromosome. Some cases occur due to having two paternal copies of chromosome 15 (about 2% of cases), mutations in the area that regulates gene expression (also around 2%), or changes in the UBE3A gene, which plays a role in protein regulation (about 5% of cases).

In about 10% of individuals with Angelman syndrome, the genetic cause remains unknown.[6] It is marked by distinct traits, including recurrent bouts of laughter, a unique

puppet-like walking pattern, lack of coordination, notable facial features, cognitive challenges, seizures, sleep issues and a specific behavioral pattern. Individuals often show delays in developmental milestones and face difficulties with learning and language skills. Most individuals with Angelman syndrome may encounter some type of seizure at some point in their lives.[7]

People with idic (15) syndrome usually present similar early signs, such as weak muscle tone, delays in development and varying degrees of intellectual disability. These developmental issues tend to range from moderate to severe. Many individuals face challenges with expressive language, often speaking very little or mostly repeating phrases they hear (echolalia). Their understanding of language can also be limited, and there may be a lack of desire to communicate, which results in minimal social engagement and repetitive behaviors. Physically, most individuals present with slight abnormalities. Together, these characteristics create a clear and identifiable neurogenetic disorder that medical professionals can recognize.[8]

CONCLUSION

This case study brings to light the behavioral, developmental, and emotional characteristics associated with Dup15q syndrome, a rare neurogenetic disorder characterized by muscle weakness, delays in development, traits related to autism, sensory sensitivities, and significant challenges in mood and behavior regulation. Symptoms such as increasing aggression, self-harm, prolonged periods of emotional dysregulation, sensitivity to sensory input, and struggles with transitions often become more pronounced as the individual ages and faces greater environmental stressors.

The patient's experience with various medications, along with ongoing rigidity and heightened emotional responses, underscores the complexities encountered in managing Dup15q syndrome, where traits of autism, mood instability, and ADHD overlap and complicate treatment. While modifications to daily routines, enhanced one-on-one support in educational settings, and careful medication oversight led to some improvement, the ongoing challenges faced by the individual highlight the need for early diagnosis, structured intervention plans, and coordinated efforts among home, educational, and healthcare environments. In summary, this case illustrates that those with Dup15q syndrome benefit from personalized, consistent, and collaborative strategies to ensure safety, enhance functional development, and improve their overall quality of life.

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