Journal Homepage: -www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI:10.21474/IJAR01/20021
DOI URL: http://dx.doi.org/10.21474/IJAR01/20021

RESEARCH ARTICLE

ANXIETY DISORDERS IN 1P36 DELETION SYNDROME: A CASE REPORT AND A CALL FOR COMPREHENSIVE PSYCHIATRIC SCREENING

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Manuscript Info

Manuscript History
Received: 07 October 2024
Final Accepted: 09 November 2024
Published: December 2024

Keywords:-
1p36 Deletion Syndrome, Anxiety Disorders, Rare Genetic Syndromes, Psychiatric Comorbidities

Abstract

Introduction: 1p36 deletion syndrome is one of the most common terminal deletion syndromes, and is often characterized by intellectual disability, global developmental delays, medical comorbidities, craniofacial dysmorphism, and behavioral abnormalities. However, psychiatric comorbidities remain underreported despite their deleterious impact on quality of life. This case report documents the manifestation of anxiety disorders in an individual with a known history of 1p36 deletion syndrome and emphasizes the need for comprehensive psychiatric screening in this population.

Case Description: This report describes a 16-year-old female with a confirmed diagnosis of 1p36 deletion syndrome, who presented with pervasive and persistent anxiety symptoms, consistent with generalized anxiety disorder, social anxiety, and performance anxiety, alongside sleep disturbances, behavioral rigidity, and executive dysfunction. Developmental history elicited global delays, moderate intellectual disability, and deficits in language and comprehension. Standardized measures confirmed the underlying anxiety disorders and comorbid ADHD, highlighting an underrecognized psychiatric phenotype within this syndrome.

Discussion: Thecase underscores the need for comprehensive psychiatric assessment in individuals with rare genetic syndromes and addresses a gap in the literature regarding anxiety disorders in 1p36 deletion syndrome. While further research is needed to understand the prevalence and management of these psychiatric comorbidities, early intervention and adopting a multifaceted therapeutic approach are paramount to mitigate the adverse psychosocial burden.

Introduction:-

Since its first description by Shapira et al. in 1997 [1], the literature acknowledges 1p36 deletion as a relatively common terminal deletion syndrome [2], reporting an estimated prevalence of 1 in every 5,000 births [3], data on the psychiatric comorbidities of the syndrome is largely lacking. The clinical manifestations associated with the syndrome and frequently reported in the literature include intellectual disability (ID), developmental delay (DD),

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seizures, behavioral oddities, seizures, distinctive craniofacial features, auditory and visual defects, pre/postnatal growth retardation, hypotonia, cardiovascular anomalies especially cardiomyopathy, and renal anomalies [4] [5] [6] [7] [8] [9] [10]. Although case reports and case series have contributed to describing the typical presentation and complications associated with the syndrome, the genetic heterogeneity of the deletions underlying the syndrome adds to the notable variability in the phenotypical presentation of affected individuals [6]. In the domain of neuro-psychiatry, while the literature stresses the intellectual disability, global developmental delay [1], and behavioral issues like self-injurious behavior, temper tantrums, etc, associated with the syndrome, the reported psychiatric comorbidities seem to be limited to isolated case reports describing Oppositional Defiant Disorder and Attention Deficit Hyperactive Disorder in affected individuals. [11] Current literature on1p36 deletion syndrome lacks reports where patients present with symptoms indicative of an underlying anxiety disorder, making this case report a novel contribution.

Case Vignette:

We present the case of a 16-year-old adolescent female with a known diagnosis of 1p36 deletion syndrome who presented at our community psychiatry clinic for her first visit to transfer care. The chief complaints, as reported by the parents, included ongoing, consistent, and substantial weight gain, sleep disturbances, behavioral issues, and rigidity. However, the most distressing concern, according to the parents, was significant anxiety, which was adversely affecting her day-to-day interactions both with family members and strangers, whom they stated she felt threatened by. The parents also described significant apprehension partaking in social interactions, consistent with social anxiety, and attested to symptoms of performance anxiety.

The patient was born after a term gestation, and the pregnancy was complicated by gestational diabetes, which was reportedly well-controlled. Her birth weight was over eight pounds, and she exhibited poor muscle tone. Additionally, the parents described several episodes of early febrile illness in the postnatal period, including urinary tract infections and ear infections. As a result, temporary tympanostomy tube placement was performed, followed by a tonsillectomy and adenoidectomy in early childhood.

A review of her past medical history reveals that she has had regular annual neurological follow-ups since the age of four. During these visits, issues with poor muscle tone since birth, difficulty socializing, communication challenges, including an underdeveloped vocabulary, and developmental delays in various growth and cognitive domains were consistently recorded. Additionally, delays in speech and walking were documented, along with abnormalities in gait and posture from early childhood. She reported receiving early speech interventions alongside occupational and physical therapy with limited improvement. Due to these developmental delays and an otherwise unrevealing diagnostic workup, the patient subsequently underwent genetic testing, which confirmed the diagnosis of 1p36 deletion syndrome. After further genetic testing of her parents yielded negative results, it was ascertained that her 1p36 deletion was most probably a de novo event.

After school initiation, neurological assessments revealed early and consistent concerns about learning difficulties, particularly in the immediate and short-term memory domains, starting at five. In response, the patient was started on Adderall, the dose for which was gradually and sequentially increased with limited improvement in symptoms. Due to a lack of response on Adderall, the patient has shifted to Vyvanse 50 mg once a day, which was eventually increased to twice a day to address the diagnosis of Attention-Deficit Disorder (ADD), along with significant difficulties in executive processing, comprehension, and organization. Supportive treatment aimed at weight management, exercise, and behavioral modification was also advised. The patient was subsequently also started on a low dose of Fluoxetine (Prozac) at 5 mg at thirteen years of age for a new-onset anxiety disorder.

When the patient first presented to our community psychiatry clinic at 16 years of age for transfer of care, it was reported that despite being on Vyvanse 50 mg, the patient experienced severe executive dysfunction, along with difficulty waking up in the morning and school refusal secondary to distress because of the underlying anxiety disorder. This anxiety was not controlled on Prozac 5 mg and had progressively worsened. The symptoms reported by the parents were further corroborated by objective assessment using the Screen for Child Anxiety-Related Disorders (SCARED) questionnaire [12].

On the child version of the scale, which was filled with assistance due to the mild to moderate intellectual disability of the patient, the patient scored a total of 41, indicating an underlying anxiety disorder (a score of 25 or higher is suggestive of an anxiety disorder with scores higher than 30 deemed more specific). Specifically, the patient scored

12 on the questions gauging the presence of Generalized Anxiety Disorder (with a score of 9 or higher being significant), 5 for the questions screening for Separation Anxiety Disorder (with a score of 5 or higher being significant), 11 for the questions assessing Social Anxiety Disorder (with a score of 8 or higher being significant), and three on the Significant School Avoidance subscale (with a score of 3 or higher being significant). The parent version of the SCARED Scale [12] also elucidated scores consistent with an underlying anxiety disorder, with a total score of 29 (above the threshold of 25 or above). The parent reported scores were significant in the domains of Generalized Anxiety Disorder (scoring 10, with nine or higher being significant) and Social Anxiety Disorder (scoring 14, with eight or higher being significant).

Additionally, according to the scoring of the NICHQ Vanderbilt Assessment Scale[13] completed by the parents, the responses confirmed Predominantly Inattentive ADHD and comorbid anxiety.

On the Wechsler Intelligence Scale for Children- Fifth Edition (WISC-V) [14], the patient obtained a composite score of 76 in Fluid Reasoning, 54 for the Full Scale-IQ portion of the scale, and 58 and 62 in Processing Speed and Verbal Comprehension, respectively. These results confirm mild to moderate intellectual disability, which led to her placement in a unique educational program to ensure that adequate resources and support could be provided.

The objective assessment based on standardized scales, as well as the symptomatology communicated by the parents during history-taking, confirmed the primary diagnosis of an anxiety disorder, particularly in the domains of social anxiety and performance anxiety alongside co-morbid ADHD (predominantly inattentive type), developmental disorder about speech, language and scholastic skills and mild to moderate intellectual disability.

Discussion:-

Whilst the literature recognizes 1p36 deletion syndrome as a relatively common [2][3] terminal deletion syndrome, much of the available literature about the disorder focuses on the medical comorbidities, craniofacial abnormalities, behavioral anomalies, and phenotypical variability of the syndrome [4] [5] [6] [7] [8] [9] [10], as well as its genetic basis [7] [15] [16]. Although focussing on these domains is essential, there is a need to highlight the paucity in the literature when it comes to the psychiatric burden of the syndrome beyond the recognition of global developmental delays and intellectual disability, which are frequently reported [4].

This deficiency underscores the broader issue regarding the often-overlooked psychiatric dimensions in rare genetic syndromes [17], which can adversely affect the quality of life of affected individuals. While experimental gene mapping studies have previously alluded to a possible link between 1p36 deletion and ADHD [18] with case reports supporting the validity of this link [11], this case report presents novel documentation of chief complaints consistent with generalized anxiety disorder [19], social anxiety disorder [19], and performance anxiety [19]in an individual with a confirmed diagnosis of 1p36 deletion.

In addition to the distress secondary to the anxiety disorders mentioned above, the patient also had developmental abnormalities in speech, language, and scholastic skills and co-morbid ADHD, alongside severe executive dysfunction, challenges with learning and comprehension as well as behavioral rigidity and mild to moderate intellectual disability. This cluster of neuro-psychiatric challenges illustrates the pervasive psychological burden and emphasizes the need for early screening and vigilant consideration of psychiatric comorbidities in those affected by 1p36 deletion syndrome.

Moreover, the authors seek to encourage the medical and research fraternity to systematically document and expand the repository of knowledge on the neuropsychiatric manifestations of 1p36 deletion syndrome and other rare genetic syndromes. The robust body of evidence generated through such unified efforts and large-scale studies can be a foundation for establishing a comprehensive and universally applicable diagnostic framework, including the aforementioned neuropsychiatric features.

Furthermore, the authors advocate for a multifaceted approach to patient care through pharmacological, psychological, and supportive therapeutic interventions.This integrative strategy should effectively address the physical and psychiatric dimensions of disorders such as 1p36 deletion syndrome, promoting holistic care and enhancing the overall quality of life.

Conclusion:-

We hereby documented the case of an adolescent female with a known diagnosis of 1p36 deletion syndrome, who presented with symptoms indicative of an underlying anxiety disorder. According to the current literature and per the knowledge of the contributing authors, this is the firstnovel report of an individual with 1p36 deletion syndrome presenting with anxiety. This case highlights the critical need for increased awareness of the often underdiagnosed and overlooked psychiatric dimensions of rare genetic syndromes. Through this report, the authors aim to add to the limited literature on the psychiatric comorbidities of the 1p36 deletion syndrome and advocate for the integration of psychiatric screening into the routine clinical evaluation of individuals afflicted with such rare genetic syndromes.

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