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Exploring the Association between Potocki-Lupski Syndrome and Autism Spectrum Disorder: A Case Report

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Abstract

Potocki-Lupski Syndrome (PTLS) is a rare genetic disorder characterized by a duplication of 17p11.2, which can lead to various congenital abnormalities and diverse behavioral phenotypes. While developmental delay and intellectual disability are commonly observed in PTLS, autism-specific traits are frequently reported as well. In this study, we present a case of a female adolescent with a de novo dup(17) (p11.2p11.2) who does not exhibit features of autism spectrum disorder (ASD). Our investigation focuses on comprehensive clinical, behavioral, and electrophysiological (EEG) evaluations. Notably, the EEG analysis revealed atypical peak–slow wave patterns and a distinctive saw-like sharp wave at 13 Hz, which have not been previously documented in other PTLS patients. The power spectral density of the resting state EEG in our patient appeared typical, but non-linear EEG dynamics, such as Hjorth complexity and fractal dimension, exhibited significant attenuation compared to neurotypical peers. Furthermore, we provide a summary of previously published reports on PTLS, highlighting the estimated occurrence of ASD (approximately 21%) which may be subject to bias due to methodological limitations. Intellectual disability and speech and language disorders were found to be more consistent features among PTLS patients.

Keywords: Speech and language disorders; Potocki-Lupski syndrome; Spectral density; Language impairments; Autism spectrum disorder; Nucleotide variants

Introduction

Potocki-Lupski syndrome is a genetic disorder that has been relatively recently identified. It is characterized by a duplication of chromosome 17 band p11.2. The length of this duplication is typically around 3.7 Mb, and it is estimated to occur in approximately 1 in 25,000 live births [1]. PTLS is associated with a broad spectrum of congenital abnormalities, including mild dysmorphic features, feeding difficulties, sleep apnea, seizures, microcephaly, and various ophthalmic, orthopedic, cardiovascular, oropharyngeal, and renal anomalies [2]. The behavioral and neurodevelopmental manifestations of PTLS are also diverse. The most common symptoms include developmental delay, intellectual disability (ranging from borderline to severe), speech and language disorders, executive function deficits, aggressiveness, anxiety, withdrawal, attention-deficit/hyperactivity disorder (ADHD), and autism spectrum disorder (ASD) features [2-4]. Initial studies suggested that ASD is a relatively common feature of PTLS, indicating a potential involvement of the 17p11.2 region in the genetics of ASD [1]. However, subsequent research has raised questions about the role of autistic features in the PTLS phenotype [5-12]. The most recent review reports a lower prevalence of ASD among PTLS patients, approximately 37.9% [2], compared to an earlier study by Treadwell-Deering et al. where the prevalence was approximately 80% based on a sample of 15 PTLS patients [1]. To contribute to the understanding of ASD in the context of PTLS, we present a case study of a 13-year-old Russian female with a confirmed de novo duplication of 17p11.2 [6]. Our investigation focuses on comprehensive clinical, behavioral, and electrophysiological assessments. Additionally, we provide an updated summary of relevant characteristics from existing literature, aiming to contribute to the ongoing discussion on the role of ASD in the PTLS phenotype [2].

Methods

To conduct a comprehensive assessment of the patient's speech, language, intelligence, and adaptive functioning, we employed a clinical interview and a battery of standardized tools. It is important to note that the Russian versions of the PLS-5 (RPLS-5) and ORRIA have not yet been normed, and since they are not suitable for the patient's biological age, we provided descriptive results for these instruments. To assess the key features of autism spectrum disorder (ASD), we utilized two methods that are considered to closely align with the gold standard of ASD diagnosis [13,14]. These methods were the Autism Diagnostic Interview-Revised (ADI-R) [15] and the Autism Diagnostic Observation Schedule (ADOS-2) [16]. The evaluations were conducted using the Russian-adapted versions of these methods [17, 18], administered by a trained clinical psychologist (OT). The final diagnosis was determined based on the discussion among the research team, following the criteria outlined in the DSM-5 TR [19].

To examine any deviations in the patient's electroencephalogram (EEG), we utilized EEG data obtained from 37 healthy controls aged between 12 and 15 years from a separate research project. The EEG data of the controls were recorded following the same protocol. The electrodes were positioned based on the international 10-10 system. EEG registration took place while the patients were awake with their eyes open during the daytime, with a total duration of 1756 seconds. The signal was sampled at 500 Hz and filtered using an online band pass filter ranging from 0.016 Hz to 70 Hz, and a notch filter at 50 Hz was applied.

EEG Analysis

For the patient, we examined an EEG segment of 1756 seconds during the eyes open condition. In the control group, each child's EEG data from the eyes open condition were analyzed for a duration of 1550

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to 2000 seconds (mean duration: 1803 ± 79 seconds). Independent component analysis (ICA) was employed, when necessary, to remove prominent artifacts [20]. Three experienced neurologists, including GP, who were certified experts, independently reviewed and interpreted the EEG data, arriving at a consensus on their findings.

To ensure comprehensive analysis, the EEG process was recorded on video to identify any typical clinical events or seizures.

The following phenomena were examined:

The presence and extent of diffuse rhythmic activity or generalized background slowing.

Epileptiform EEG abnormalities: a. Sporadic wave discharges, spikes, and multi-spikes were categorized as benign focal epileptiform discharges of childhood without clinical manifestations. b. Episodic peak-wave or slow spike-wave complexes, which lacked repetitive structure, generalization, or secondary generalization, and were not accompanied by clinical events. The topography of this activity was also taken into consideration. c. Typical or atypical epileptiform discharges displaying secondary generalized spike-slow wave discharges or spike-wave discharges that either correlated or did not correlate with clinical events.

To explore the prevalence of ASD in individuals with Potocki–Lupski syndrome (PTLS) and analyze existing literature on the topic, we conducted a systematic search in the PubMed database. Relevant articles were identified using the search terms "(Potocki-Lupski) AND (autis OR ASD)" applied to titles and abstracts, limited to studies published in English. Additionally, articles from a previous literature review [2] were included if they were not already identified in the PubMed search. Several exclusion criteria were applied, including: (1) articles that were not in full text format (such as letters and conference theses); (2) studies without original data, including various types of reviews and meta-analyses; (3) animal studies; (4) studies based on group comparisons; and (5) studies involving participants below 18 months of age, as a reliable diagnosis of ASD is not feasible at such early ages [21-23].

Case presentation

The child does not have any siblings, and the pregnancy was free from complications. There were no reported instances of infections, medication usage, smoking, alcohol consumption, or drug intake during pregnancy. At the time of the child's birth, the mother and father were 34 and 30 years old, respectively. There have been no known genetic syndromes in the family. The child was delivered in the 42nd week of gestation due to artificially induced labor caused by an abnormally slow heartbeat and excessive fluid in the lungs. Consequently, she was admitted to a neonatal intensive care unit. The birth weight was 2920 g, which falls within the 25th percentile. From the early months of life, the child encountered multiple difficulties, including failure to thrive, feeding problems characterized by poor sucking and vomiting after meals, and sleep disturbances. During early childhood, she experienced episodes of breath-holding spells with loss of consciousness and febrile seizures associated with high fevers exceeding 40°C. Gross motor milestones were achieved towards the later end of the normal range, with walking attained at 14 months, although initially, it was unsteady. Fine motor skills remained challenging for some time. Bowel and bladder control were delayed and achieved at 40 months. In terms of language development, there was no history of babbling, and her initial vocalizations were described as "whistling" sounds. She began saying her first words at approximately 18 months, but they were sporadic, and she did not consistently use stable words until she was three years old. It wasn't until four years of age that she started forming simple three to five-word phrases. Additionally, she experienced significant delays in receptive language skills. At four to five years old, she understood approximately 50 words but struggled to follow complex instructions. Her parents found it necessary to break down instructions into smaller parts. Notably, her understanding of language appeared to rely more on context than the meaning of phrases. Furthermore, her own speech was challenging for others to understand due to international issues and a limited vocabulary. By the age of five, she received diagnoses of developmental delay, sensory-motor, ADHD, speech and language impairments, and several learning disorders such as dyslexia, dysgraphia, and dyscalculia. The child's mother also mentioned that clinicians who assessed her noted traits of ASD. The child was initially referred to the research team at the age of 11 for a comprehensive evaluation, which revealed delays in speech and cognitive development, difficulties in adaptive functioning, and concerns about the genetic basis of her conditions. Later, at the age of 13, genetic testing was recommended, and the family trio underwent whole-exome sequencing (WES) to analyze their genomes. The analysis identified multiple de novo single nucleotide variants (SNVs) and copy-number variations (CNVs), two of which were clinically significant: a deletion in the 15q11.2 region and duplication in the 17p11.2 region. Molecular cytogenetic testing using fluorescence in situ hybridization (FISH) did not confirm the presence of the 15q11.2 deletion. However, the 17p11.2 duplication was confirmed, leading to the diagnosis of Potocki–Lupski syndrome. The patient's clinical presentation aligns closely with the main features of the syndrome, including multiple developmental delays, muscle hypotonia, feeding difficulties, and behavioral disorders.

At the age of 13, the patient was enrolled in a regular public school and received education through an individualized plan in inclusive settings, primarily designed for children with ASD. However, her parents observed persistent difficulties in comprehending spoken language and experienced challenges with pronunciation, intonation, and fluency. Academically, she was described as falling behind, as she had recently started developing writing skills and faced difficulties in arithmetic and memorization. The patient's mother characterized her as highly sociable, friendly, and trusting. She exhibited a strong attraction to people, displayed high levels of empathy, and thoroughly enjoyed engaging in play with peers, particularly in storytelling and role-playing activities.

Language improvement

The patient's performance on the RPLS-5 assessment revealed significantly lower scores compared to her peers. She achieved raw scores of 56 out of 65 for Auditory Comprehension and 54 out of 67 for the Expressive Communication subscales. Her overall language ability in Russian was equivalent to that of a five-year-old and two-month-old child, although caution is warranted since the norms used were based on English-speaking populations only.

Discussion

In this case report, we present a detailed evaluation of a female patient with PTLS, focusing on clinical, behavioral, and electrophysiological aspects, particularly regarding the features and associations of ASD, which is commonly observed in this syndrome. The reported prevalence of ASD among individuals with PTLS varies from 37.9% to 80% [24]. This range appears to be wider compared to other common genetic syndromes, where the prevalence of ASD ranges from 11% to 61%, as shown in a systematic review and meta-analysis conducted in 2015 [25].

However, it is worth noting that there are cases of individuals with PTLS who do not exhibit autistic features or only show some features that do not align with a complete clinical picture of ASD (refer to Table A1). Consequently, the study by Ercan-Sencicek et al. [5] questioned the central role of autism-related features in PTLS. Instead, they proposed that speech and language disorders may play a more significant role. Thus, it is possible to consider that communication difficulties in PTLS patients may not solely represent "true" ASD but could be associated with language impairments. In terms of receptive language skills, the patient encountered challenges in following complex instructions consisting of three steps, understanding certain logical operators (such as "before" and "then"), grasping prefixes, recognizing rhymes, and comprehending the sound composition of words. Additionally, she struggled with answering questions related to story comprehension. Regarding expressive communication, the patient demonstrated the ability to construct complex sentences consisting of four to five words and engage in conversations about her toys and significant life events. However, she faced difficulties when it came to explaining the usage of objects, providing reasons, and understanding consequences. Results from the ORRIA assessment highlighted specific weaknesses in sentence repetition, as the patient frequently repeated only the last word in a sentence when tasks became more numerous and complex. Additionally, she encountered challenges in items assessing working memory abilities and the mastery of complex semantic structures involving logical, temporal, and spatial relationships.

Conclusion

This case study contributes to the existing knowledge on the phenotypic manifestations of PTLS, a relatively rare and newly recognized genetic condition. Although ASD is commonly associated with PTLS, our patient did not exhibit this disorder. Instead, she presented with cognitive delay and language impairments as the prominent features. The analysis of the patient's clinical EEG revealed atypical peak-slow wave patterns and a unique saw-like sharp wave at a frequency of 13 Hz, which has not been previously reported in the literature we reviewed. However, when examining the power spectral density of the resting state EEG using PSD, no significant differences were observed between the patient and a cohort of healthy individuals. Nonetheless, the patient exhibited lower values of non-linear features, such as Hjorth complexity and fractal dimension, compared to her neurotypical peers.

A scoping review of the literature on PTLS cases revealed that intellectual disability was the most commonly reported behavioral and psychiatric diagnosis, followed by various types of speech and language impairments, and then ASD.

Acknowledgement

Not applicable

Conflict of Interest

None

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