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Case Report

Novel *PRKAR1B* Variant Responding to Topiramate in a Lebanese Child

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Abstract

Patients with *PRKAR1B* gene variants can present with a neurodegenerative disease in adults or a cognitive delay, behavioral problems and regression in children causing Marbach-Schaaf Neurodevelopmental Syndrome (MASNS) which is a rare autosomal dominant disease. However with less of 30 reported cases in Literature, the clinical spectrum of *PRKAR1B* gene mutations remains to be explored, and the treatment remains challenging. In this paper, we report the cases of a Lebanese child with previously unreported missense *PRKAR1B* variant presenting with a massive arachnoid cyst, speech delay, cognitive delay, behavioral dysregulation and developmental regression at 2 years of age. The patient showed behavioral response to treatment with a low dose of topiramate. This case expands the known genotypic and phenotypic spectrum of this recently described disorder, highlighting the importance of genetic investigation in children with cognitive delay.

Keywords: *PRKAR1B, Marbach-Schaaf Neurodevelopmental Syndrome, Global Developmental Delay, Autism Spectrum Disorder, Whole Exome Sequencing, Topiramate, Arachnoid cyst.*

Introduction

Pathogenic variants in the *PRKAR1B* gene, which encodes the RIβ regulatory subunit of protein kinase A (PKA), have recently been identified as the cause of Marbach-Schaaf Neurodevelopmental Syndrome (MASNS). PKA is a fundamental enzyme in the cAMP signaling pathway, acting as a crucial mediator of neuronal signaling and synaptic plasticity, specifically Long-Term Potentiation and memory formation [1,2,3].

The clinical presentation of MASNS in children is characterized by global developmental delay, intellectual disability, severe speech delay or regression, and a high prevalence of autism spectrum disorder (ASD) and ADHD traits. Unlike the *PRKAR1B* p.Leu50Arg variant, which leads to protein aggregation and adult-onset neurodegeneration [4], the variants associated with MASNS typically result in a loss of function or haploinsufficiency, disrupting neurodevelopment rather than causing neuronal death [1,5]. This disruption specifically impairs the "synaptic learning" mechanisms in the hippocampus, leading to the cognitive and behavioral phenotypes observed in patients [6].

To this day, the Lebanese population maintains a high rate of consanguinity, which increases the likelihood of identifying rare genetic etiologies for neurodevelopmental disorders [7,8]. However, *PRKAR1B*-associated disorders have not yet been systematically reported from this region. Here, we report a Lebanese child carrying novel *PRKAR1B* variant (783G>T) who presented with autism-like symptoms and developmental regression.

Case Presentation

Here we report a 7-year-old male born at term by elective cesarean section after an uncomplicated pregnancy, to first degree consanguineous parents from South Lebanon (Figure 1) with normal neonatal adaptation and appropriate early developmental progress. A history of cognitive delay is noted in the paternal uncle. Early motor and language milestones were achieved within expected timeframes: independent walking occurred at approximately 1 year of age, and first words were produced around the same period. By 2 years of age, the child was forming two-word sentences and demonstrated an expressive vocabulary of approximately 60 words.

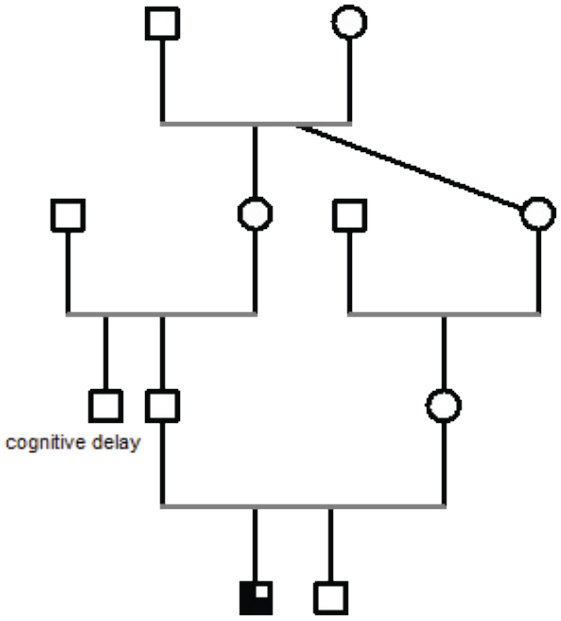

Figure 1. The patient's family pedigree.

At 2 years and 6 months, a significant regression in expressive language developed. Spoken language gradually diminished, resulting in marked impairment in communication. No acute illness or identifiable trigger were documented during this period. Despite preserved nonverbal reasoning abilities, expressive communication declined to the extent that the child functioned as a non-speaking individual. During the same interval, behavioral dysregulation emerged, including frequent tantrums, agitation, hyperactivity, and oppositional behaviors.

The patient presented always a normal neurological exam, with no focal deficit, and a normal clinical exam with normal growth parameters.

The patient started to receive speech therapy and psychomotor therapy sessions for more than three years. Gradual improvement was observed over time. By 5 years of age, spoken language began to re-emerge, eventually progressing to two-word phrases. the child started to show strong cognitive potential with appropriate problem-solving capabilities as well, but expressive language limitations and behavioral difficulties remained prominent.

The Brain MRI showed a large left middle cranial fossa arachnoid cyst (5.2 × 5.4 × 6 cm, Galassi type II) causing mass effect on the temporal lobe and insular region, with mild collapse of the left lateral ventricle and displacement of the Sylvian fissure. Repetitive brain imaging over 3 years showed a stability of the Cyst, necessitating no intervention. (Figure 2)

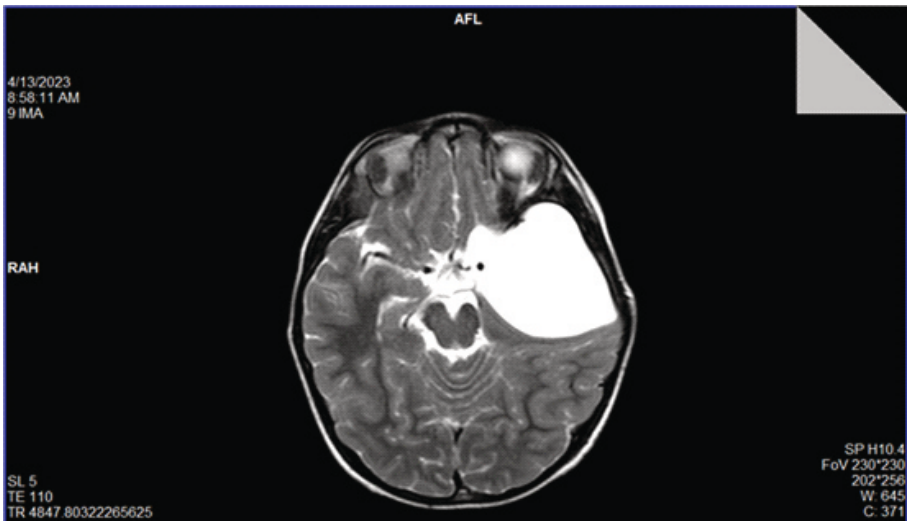

Figure 2. Brain MRI: large left middle cranial fossa arachnoid cyst (5.2 × 5.4 × 6 cm, Galassi type II)

With a baseline metabolic work up showing no anomalies, Whole Exome Sequencing (WES) was pursued. Genetic analysis identified a previously unreported gene variant in *PRKAR1B* (783G>T). The mutation was not found in either of the parents.

Despites the partial improvement in speech acquisition, the patient continued the have frequent episodes of tantrums, agitation, his hyperactivity was affecting his attention capacities, combined with his opposition disorder. The patient did not show any clinical improvement while on treatment by risperidone, Atomoxetine or Amitriptyline. A treatment by low dose of topiramate 2 mg/kg/day improved the behavioral and cognitive functions of the patient, leading to psychological stability allowing the improvement of the cognitive acquisition capacities and improving the patient's attention, leading to a noticeable improvement in the learning curve and specially the linguistic acquisitions during the speech therapy sessions.

Discussion

Here we report a Lebanese child presenting with neurodevelopmental regression, behavioral dysregulation, and expressive language deficits. Whole Exome Sequencing (WES) identified novel variants in the *PRKAR1B* gene, implicating Marbach-Schaaf Neurodevelopmental Syndrome (MASNS). The clinical features observed in this patient align with the established developmental profile of the syndrome while suggesting an expansion of the genotypic spectrum described in recent literature [9].

A defining feature of MASNS is global developmental delay often accompanied by intellectual disability [1]. It is also associated with Adult Neurodegeneration in specific variants (p.Leu50Arg). and this patient presents the distinct pattern of early normal development followed by regression between 24 and 30 months of age.

This patient experienced a loss of vocabulary, and a decline in expressive language. This is consistent with the initial cohort described by Marbach et al., where severe speech delay was universal [1]. The recovery of language in this child at age 5 supports the hypothesis that *PRKAR1B* loss-of-function causes a "synaptic arrest" rather than permanent cell death. This is corroborated by murine models showing that loss of the R1β subunit specifically abolishes Long-Term Potentiation and Depotentiation in the hippocampus, mechanisms required for consolidating new information, without causing gross anatomical defects [6].

The majority of genetically confirmed MASNS cases harbor the recurrent missense mutation c.1003C>T (p.Arg335Trp), which creates a "dominant-negative" protein that blocks PKA activity [1,10].

In this case, the reported variant *PRKAR1B* (783G>T) is a missense variant that affects a structural domain resulting in haploinsufficiency [5] leading to decreased synaptic formation, which can be amplified by the lack of stimulation and the prolonged screen exposure that is a current practice in today's society. And with the extensive rehabilitation therapies, speech therapy, psychomotor therapy and occupational therapy, within a specialized environment, the patient was able to recover progressively his lost competencies, unlike the other reported patients in literature. This finding can be explained by the phenotypical variation of mutations, but also by the response to intensive stimulation, suggesting a limited synaptic dysfunction.

This is also the first reported case of a patient with *PRKAR1B* variant presenting with a massive arachnoid cyst, which can be a consequence to a neural crest development dysregulation. A research by Sakai et al. in 2006 suggests that PKA signal facilitates Sox9/Snail2 function to promote neural crest formation and epithelial-mesenchymal transition, a dysregulation in the PKA function can theoretically lead to the neural crest malformation leading the reported arachnoid cyst. [11,12,13]

A normal neurocognitive development was clearly noted in this patient, with a dramatic regression around the age of two years, this can be explained by the synaptic depression leading to synaptic plasticity impairment [1], and the decreased long term hippocampal potentiation [14,15] while keeping in mind that some variants of this gene can results in a Neuronal intermediate filament inclusion disease [3]. And based on the synaptic theory we can explain the clinical response to behavioral therapy rather that to medication, since rehabilitation therapy acts mainly on synaptic formation and cortical maturation [16].

Even though Topiramate is not the first line treatment for behavioral problems in children, but it can be very effective and well tolerated for managing disruptive behavioral problems and emotional instability in children and adolescents [17]. In this patient a clear behavioral improvement was noticed after the introduction of topiramate, while first class treatment failed to produce any significant change. The response to topiramate treatment in this patient can be explained by the ability of topiramate to interact with ion channel PKA phosphorylation sites, thus regulating its functions, since the inhibition of the PKA increases the Topiramate potentiation of the GABA receptors [18]. Further trials would be beneficial in exploring the long-term effect of Topiramate on the psychological and cognitive functions in patients with *PRKAR1B* variants.

Even though Marbach–Schaaf syndrome is characterized by developmental delay, intellectual disability, autism- spectrum disorder, pain insensitivity, and mild dysmorphisms [5], in our patient pain insensitivity and dysmorphism were not observed. The child also had normal height and weight without any signs of hyperphagia as reported in literature. These findings help broaden the phenotypical spectrum of the patients with *PRKAR1B* variants.

Conclusion

Here, we report the case of a Lebanese child bearing previously unreported heterozygous variants in *PRKAR1B*, presenting with early speech delay or language regression, autism spectrum disorder–like features, and prominent behavioral disturbances responding to topiramate, and a massive arachnoid cyst. These findings widen both the mutational and clinical spectrum of *PRKAR1B*-related neurodevelopmental disorder, supporting recent literature suggesting the genetic etiology extends beyond the recurrent p.Arg335Trp mutation [5,9].

Recognition of the diverse clinical characteristics described here may help direct clinicians toward early genetic testing. Consequently, our findings suggest that *PRKAR1B*-related disorder should be included in the differential diagnosis of childhood speech delay and behavioral dysregulation specially in the context of regression, despite its rarity, to ensure early identification. Early intervention should be considered as essential in improving the cognitive outcome of these patients. Treatment with low dose topiramate can be beneficial for these patients presenting with severe behavioral problems.

Conflict of Interest

None of the authors has a conflict of interest with the material presented in this paper.

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