Clinics in Neurology

ISSN: 2692-7934

Case Report

# Potocki Lupski Syndrome with Carnitine Deficiency in a Lebanese Patient

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## Abstract

Potocki Lupski Syndrome (PTLS) is a rare hereditary multisystem disorder, attributed to micro-duplication on the short arm of the chromosome 17. Phenotypic features vary remarkably from one patient to another including, cognitive delay, dysmorphic facial features and autistic like behaviors.

Here we report the case of a 2 years 9 months old Lebanese female patient presenting with Potocki Lupski Syndrome, this patient showed carnitine deficiency and secondary mitochondrial dysfunction associated with her disease. A trial of L-carnitine supplementation was initiated as part of management, resulting in a significant rapid overall improvement of the patient's cognitive functions.

**Conclusion:** Secondary mitochondrial dysfunction should be investigated in patients with PTLS, a rapid cognitive and behavioral response can be expected upon appropriate supplementation.

**Keywords: Potocki lupski syndrome, mitochondrial disease, carnitine deficiency, RAI1 gene**

## Introduction

Potocki Lupski Syndrome (PTLS) is a rare developmental disorder caused by a heterozygous duplication of the 17p11.2 chromosome with an incidence of 1 in 25000 births [1,2]. This mutation was first described in 1996 and best understood in 2007 [2]. The mutation either arises as de novo or it can be inherited in an autosomal dominant fashion [1]. The syndrome remains hard to recognize because it presents with very nonspecific symptoms [3]. PTLS patients present with neuro developmental findings, congenital heart disease, with failure to thrive and mildly to moderate dysmorphic facial features. A definite diagnosis is then established through identification of a heterozygous duplication at chromosome 17p11.2 encompassing RAI1 gene [2]. The main clinical aspects observed with PTLS are in the early age, hypotonia, poor feeding, and Failure to Thrive (FTT), congenital cardiovascular anomalies, and sleep-disordered breathing, older children present with developmental delay, cognitive impairment and abnormal behavior. The most common presenting signs are hypotonia and FTT [4]. Speech abnormalities are generally present in the majority of PTLS patient's with intonation difficulties, speech delay, prosody and verbal apraxia. Atypical behavior is also common and frequently classified under the umbrella of Autism Spectrum Disorders [3]. Here we report the first Lebanese patient with PTLS, with associated mitochondrial dysfunction, improving on L-carnitine supplementation.

**Citation:** Mansour H, Choucair M, Charrouf D, Nassour N, Zahed L. Potocki Lupski Syndrome with Carnitine Deficiency in a Lebanese Patient. Clin Neurol. 2020;1(1):1005.



**Publisher Name**: Medtext Publications LLC

**Manuscript compiled:** Mar 28th, 2020

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## Case Presentation

Here we report the case of a 2 year 9 months old female patient born to term by caesarian section to nonconsanguineous parents referred to pediatric neurology clinic for developmental delay. The patient had a history of failure to thrive thoroughly investigated, without any underlying defined biological cause. Developmentally, the patient was poorly active before 1 year of age, with poor interaction and reactivity to stimulation. She started to walk at 1-year 7months, and no speech was acquired by the age of 1 year 6 months, then some babbles started to be noted by the parents.

On physical exam the patient was very passive but with a smart gaze, and a good capacity of observation, without spontaneous interaction, not responding to her name when called, and throwing tantrums easily when she was not able to express herself, and was only able to say 5 basic words used out of context as simple repetitions. The patient a very unorganized sleeping pattern. She had down slanting palpebral fissures and microcephaly with a head circumference of 46 cm (3rd percentile). The patient had a good muscle tone, normal motor strength, poor fine motor skills, unsteady and unstable gait, stumbling easily, with frequent falls, difficulty alternating and a very poor coordination, with the inability to climb stairs easily and an inability to catch the ball adequately.

To note that the patient has been taking regular sessions of speech and psychomotor therapy (three times per week each) that was started one year prior to presentation, with no significant improvement.

A metabolic and radiological work up was done and showed mild decrease in carnitine blood level (total carnitine 30 (Normal 43 miccromol/l to 65 miccromol/l) Free carnitine 15(30 micromol/l to 50 micromol/l)), normal regular Karyotype, the chromatography of amino acids showed mild increase in alanine 404 micromol/l (>343 micromol/l), Chromatography of organic acids in urine noted increase in glyceric acid 65 mg/g crea) normal <9. Brain MRI with spectroscopy showed no abnormalities. A cardiac Ultrasound was done and showed mild aortic regurgitation (grade 1 of 4).

The study was completed with next generation sequencing, and the cytogenetic test showed a large one copy gain of a 3.6 Mb region in cytoband 17p11.2 that had been identified by whole exome sequencing and subsequently confirmed by chromosomal microarray analysis. The copy number gain overlaps significantly with Potocki Lupski Syndrome. Meanwhile no mutation in the genes responsible for the mitochondrial diseases or the carnitine metabolism were found, so the findings were attributed to a secondary carnitine deficiency, and the patient was started on carnitine treatment with 100 mg/kg/day divided in 2 doses, and the speech and psychomotor therapies were maintained with the same team as previous at the same rate.

After 2 months the patient showed significant improvement in her motor skills, the patient showed a normal steady gait, alternating legs, was able to climb stairs easily, and had much better overall activity. She was also able to use a scooter with accurate coordination of the legs.

On the 3 months follow up the parents reported that she had a regular sleeping pattern, became much calmer during outings, she would respond to her name when called, she no longer threw as much tantrums as in the past and was able to be reasoned with when angry or irritated; the parents were able to better communicate with their child as she showed much improved communication skills. The patient was showing improved language skills: she was able to imitate easily others, and was able to use 20 different words in their right context as well as correctly name animals and imitates sounds.

## Discussion

In a society with a very elevated rate of consanguinity, like Lebanon [5], rare disorders are more common than in western populations [6,7] and their management doesn't follow the regular known practices, and they are included more frequently in the lists of differential diagnosis. A diagnosis of autism should always be studied beyond the psychiatric aspect, especially that in our population multiple rare disorders can be expressed in the same patient at the same time [8]. Even though no specific treatment for PTLS has been described until present, but the diagnosis of the associated mitochondrial dysfunction in this patient allowed to speed the cognitive improvement.

Potocki-Lupski Syndrome (PTLS) is characterized by a group of manifestations including dysmorphic features, abnormal behaviors and delayed cognition. Early presentations can range from an asymptomatic newborn with a small head circumference to an infant with congenital heart disease. These symptoms might be subtle until later in life, when patient might present with intellectual disability or failure to thrive [9,10]. According to the data presented by Bissell et al. [11] both PTLS and idiopathic ASD patients had overlapping repetitive and stereotypical behavioral patterns associated with defective social interaction skills, but to a lesser extent.

Patients with this syndrome significantly vary phenotypically and might be missed by many physicians, leading to under diagnosis, and to the labelling as autistic, inattentive or hyperactive [3]. It is essential to keep a high index of suspicion of an underlying cause when presented with patients suffering of mental delay and/or behavioral problems, especially in the presence of systemic manifestations [12]. The next generation sequencing techniques have made this diagnosis easier when the clinical signs are missed by the primary physicians [13], especially when de novo mutations are present, and in diseases with multiple overlapping symptoms [14,15].The diagnosis of this syndrome is confirmed by genetic studies, revealing duplication at the chromosome 17p11.2. Chromosomal Micro Arrays (CMA) is the most preferred genetic analysis, as part of investigation for a patient with neuro developmental delay, multiple systemic abnormalities and autism spectrum disorders [16]. Prenatal diagnosis has been reported in the literature in 2012 by Popowski et al. [2] and Bravo et al. [9], respectively.

When identified, early intervention can positively influence outcome in PTLS patients. A multidisciplinary specialist team [3] should include in addition to the pediatric neurologist, a speech therapist, a psychomotor therapist, an occupational therapist an ophthalmologist, an ENT specialist, a cardiologist, and urologist.

In the previously reported cases the secondary mitochondrial dysfunction was not investigated nor exploited, but in 2017 Mullegama et al. [17] showed that the over expression of the Retinoic acid induced 1 (RAI1) gene results in a major hypothalamic dysregulation in patients with PTLS syndrome, as opposed to the haplo insufficiency of the same gene resulting in a similar hypothalamic dysregulation in Smith-Magenis syndrome as described also by Vetrini et al. [14].

This dysregulation leads to the cognitive, behavioral changes altered motor and sensory coordination, growth retardation, sleep disturbances and hypotonia as well feeding habits alterations and increased levels of anxiety [18]. Also, the dysregulation of the mitochondrial function in the hypothalamus can lead multiple metabolic diseases, with symptoms similar to these symptoms especially in the nutritional aspect [19].

In this patient the secondary mitochondrial dysfunction was suspected with the mild carnitine deficiency and the increase in glyceric acid in the urine that can be secondary to the mitochondrial respiratory chain dysfunction [20] or secondary to carnitine deficiency, as well as the elevation of the alanine that can be found in patients with mitochondrial dysfunction [21]. Another possible explanation for the L-carnitine deficiency can be due to the already present failure to thrive as described in literature [22] especially with the unusual feeding habits in PTLS patients.

The main etiology of this mitochondrial dysfunction remains to be discussed, it can be a part of the PTLS especially in the hypothalamic dysregulation secondary to the RAI1 over expression, or it can be secondary to the carnitine deficiency, due to FTT and poor supplementation following the unusual feeding habits. This mitochondrial dysfunction remains to be investigated in a larger population of children affected with PTLS, since it can offer a simple therapeutic possibility for these patients.

The correction of this carnitine deficiency and the ensuing mitochondrial dysfunction led to a rapid cognitive improvement in this patient. This improvement can be mainly due to the improvement of the hypothalamic dysfunction in this patient with the improvement of the sleep pattern, which also increased the attention capacity during the therapy sessions.

## Conclusion

In this article we have presented the first reported PTLS patient in the Lebanese population. The syndrome remains hard to recognize because it presents with very nonspecific symptoms, and should be included as a differential diagnosis in patients classified under the autism umbrella. The definite diagnosis can be achieved with next generation sequencing. Secondary carnitine deficiency and a possible mitochondrial dysfunction should always be considered, and a trial of

carnitine supplementation should be started, with an expected rapid improvement of the cognitive function.

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