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Case study

# Atypical presentation of Costeff syndrome-severe psychomotor involvement and electrical status epilepticus during slow wave sleep

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ABSTRACT

*Background:* Costeff syndrome or OPA3-related 3-methylglutaconic aciduria is an autosomal recessive neurodegenerative disorder characterized by early onset optic atrophy and choreoathetosis with later onset of ataxia and spasticity. Costeff syndrome is prevalent among Iraqi Jews.

*Methods:* We describe a 5 year old girl from Syrian Jewish origin with an atypical presentation of Costeff syndrome.

*Results:* The patient presented with asymmetric optic atrophy, severe dystonia and choreoathetosis and global developmental regression at the age of 7 months; no achievement of independent walking and only minimal speech; and appearance of electrical status epilepticus during slow wave sleep in the second year of life with further deterioration. She harbors the classic mutation (c.143-1G > C) in the *OPA3* gene.

*Conclusion:* Costeff syndrome may present in an atypical manner regarding the ethnic origin, clinical manifestations and co-occurrence of epilepsy. Mutations in *OPA3* should be evaluated in all cases presenting with the core features of typical Costeff syndrome.



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## 1. Introduction

Costeff Syndrome or OPA3-related 3-methylglutaconic aciduria or 3-Methylglutaconic aciduria type III is one of the 5 groups of 3-Methylglutaconic aciduria (MGA) which encompasses a heterogeneous group of disorders, coinciding with elevated levels of urinary 3-MGA. Costeff syndrome is characterized by optic atrophy and an extrapyramidal movement disorder presenting in childhood. Optic atrophy is associated with decreased visual acuity within the first years of life, sometimes associated with infantile-onset horizontal nystagmus. Most individuals have chorea, often severe enough to restrict ambulation. Progressive spasticity and cerebellar ataxia are variably seen in affected children and are more common at later stages. The intelligence is usually within the normal range.[1–3]

The diagnosis is suggested by elevated urinary excretion of 3-methylglutaconic acid (3-MGA) and confirmed by identification of biallelic *OPA3* pathogenic mutations. The syndrome is inherited in an autosomal recessive manner. It is almost exclusively described in Iraqi Jewish descents, which have a single pathogenic variant (c.143-1G > C) in all affected patients.[3] This mutation is suspected to cause mitochondrial dysfunction.[4]

Epilepsy with continuous spikes and waves during slow-wave sleep is an age-related epileptic encephalopathy that is characterized by (1) seizures, (2) an electroencephalography (EEG) pattern of electrical status epilepticus during sleep (ESES), and (3) neurocognitive regression. It can represent an atypical evolution of benign epilepsy with centro-temporal spikes (BECTS) or other "benign" focal childhood epilepsies. It also occurs in children with malformations of cortical development, hydrocephalus or thalamic lesions.[5]

We describe a girl with Costeff syndrome who presented in the first year of life with atypical manifestations including early developmental regression followed by epilepsy with CSWS and further behavioral and cognitive deterioration.

## 2. Case study

The patient is the 5 year old daughter of healthy parents from consanguineous, Jewish Syrian origin. She has 2 healthy brothers and no family history of neurological diseases. She was born in Argentina after an uneventful pregnancy. Perinatal history and development until the age of 7 months were described as normal.

At the age of 7 months she developed extrapyramidal movements including dystonia and chorea and gradually lost developmental milestones: the ability to reach out for toys, clapping hands and sitting. An ophthalmologic examination revealed a unilateral pale optic disc consistent with optic atrophy.

She underwent a thorough metabolic evaluation which was normal except for elevated excretion of urinary 3-MGA. A muscle biopsy showed normal pathology and respiratory chain enzyme function. A karyotype was normal. An EEG at ten months of age and a brain MRI were normal.

The elevated 3-MGA, together with a clinical phenotype of an extrapyramidal movement disorder, optic atrophy and her Jewish origin raised the suspicion of Costeff syndrome and she was referred for further investigation to our metabolic neurogenetic clinic in Israel. Quantitative urinary organic acids repeated twice in Israel was normal and did not show elevation of 3-MGA. Genetic testing for the *OPA3* mutation using restriction enzymes and gene sequencing confirmed homozygosity for the c.143-1G > C mutation.

At the age of 17 months she presented with focal dyscognitive seizures manifesting as brief staring spells, sometimes associated with head and eye deviation. EEG's showed bilateral multifocal central, temporal, occipital and parietal epileptic activity. Despite antiepileptic treatment with clobazam and levetiracetam the seizures continued and were accompanied by behavioral deterioration. She became withdrawn and lost non verbal communication. At the age of 26 months a video EEG demonstrated mid paracentral and temporal spikes clinically correlating with events of halting motor activity during wakefulness. During sleep there was a marked potentiation of the epileptic activity with bilateral and bisynchronous sharp-slow-wave discharges occupying 85% of the total duration of NREM sleep (Fig. 1), consistent with the diagnosis of ESES. Treatment with valproic acid, sulthiame and levetiracetam did not lead to satisfactory improvement. Pulse therapy with high dose methylprednisolone and intravenous immunoglobulins given monthly for 6 months were effective and the ESES abated. The seizures ceased and she became more alert, active and communicative. A follow up EEG revealed predominantly right centrotemporal epileptic activity during sleep occupying less than 50% of the time.

The Mullen Scale of Early Learning was administered at the age of 3 years and revealed a gross motor scale at the level of 9 months, fine motor and receptive language scales at the level of two years, expressive language was consistent with no achievement of speech ability.

On examination at the age of 5 years her head circumference, weight and height are on the second percentile. She has temporal pallor of the optic discs, convergent strabismus with no ophthalmoplegia or nystagmus. General tone is low but the resistance in the ankles is increased, muscle strength is normal as well as tendon reflexes. She displays choreoathetotic movements involving her face, neck and limbs. She crawls on her belly, and sits independently. She does not stand or walk. When she attempts to stand or walk her choreiform movements increase and she shows scissoring. She can insert simple shapes into a board, she holds a pencil and scribbles but she cannot build with cubes. She is communicative and understands simple instructions and can point to a few body parts. She does not have any effective speech due to severe dysarthria, but has started to utter syllables. She is not toilet trained. She currently receives medical treatment with trihexyphenidyl and clobazam. She attends a special education kindergarten. Comparative genomic hybridization was normal.

## 3. Discussion

We describe a child with an atypical presentation of Costeff syndrome regarding ethnicity, laboratory results, clinical manifestations and natural history.