A Case of Recurrent Fever, Unilateral Weakness, and Encephalopathy

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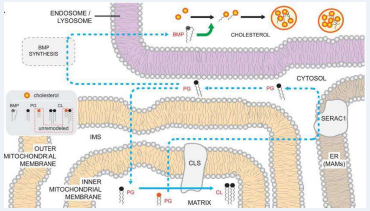
Introduction

The SERAC1 gene encodes a protein which is involved in the remodeling of the phospholipid phosphatidylglycerol. Phosphatidylglycerol is found at the interface between mitochondria and endoplasmic reticula, and is a precursor for cardiolipin, which is essential for proper mitochondrial function, and for bis(monoacylglycerol)phosphate, which is essential for intracellular cholesterol trafficking [1]. Mutations in the SERAC1 gene impair mitochondrial function, and are most commonly associated with MEGDEL syndrome, 3-methylglutaconic aciduria with deafness, encephalopathy, and Leigh-like syndrome.



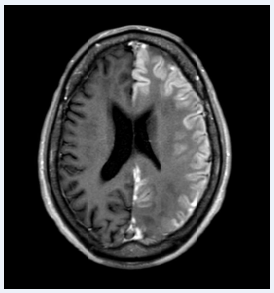
1. Function of SERAC1

Patients with MEGDEL syndrome typically present in childhood with developmental delay, spasticity, dystonia, seizures, optic atrophy, and sensorineural hearing loss. Imaging typically shows generalized atrophy with lesions in the basal ganglia. Laboratory testing shows 3-methylglutaconic aciduria. Some patients present later in their adolescent years or in early adulthood with mild cognitive impairment or juvenile-onset spasticity, suggesting a spectrum of clinical presentation. Here, we present a different phenotype altogether from what has previously been described in association with SERAC1 mutations.

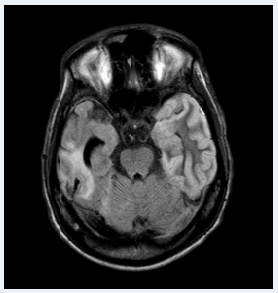
Case Presentation

A 25 year-old Hispanic male with a past medical history of retinitis pigmentosa began having recurrent episodes of encephalopathy, nausea, vomiting, fever, and unilateral weakness or parasthesias at the age of 17. These episodes typically lasted three to four days after which he would recover back to his baseline. He had experienced a total of three episodes prior to his presentation to our facility, and had been given a possible diagnosis of MELAS, although he had never undergone genetic testing or muscle biopsy.

He initially presented to an outside hospital with headache, vomiting, confusion, and high-grade fevers to 103ºF. He was mildly tachycardic, and had a lactic acid of 3, and was empirically started on antibiotics. He was encephalopathic,



2. MRI brain post-contrast showing left hemispheric edema, and gyral and leptomeningeal enhancement

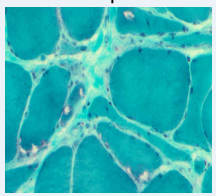


3. MRI brain T2 FLAIR showing right temporal lobe encephalomalacia

but could still follow commands. Four days into his admission, he developed right sided weakness and was subsequently given tPA. MRI brain was negative for infarct, but did reveal unilateral left hemispheric edema, and gyral and leptomeningeal enhancement [2], as well as right temporal lobe encephalomalacia [3]. He continued to spike high-grade fevers despite antibiotics, and infectious work-up returned unrevealing. Over the next five days, he continued to deteriorate clinically to the point of requiring intubation, at which point he was transferred to our facility for further care.

Shortly after transfer to our facility, the patient began having clinically-evident generalized and right-sided focal motor seizures with no EEG correlate. These seizures remained intractable for almost two weeks and eventually were controlled with Vimpat and Fycompa. Repeat MRI revealed worsening left hemispheric edema, for which he was given five days of pulse steroids and slowly tapered off. CSF studies revealed elevated protein, but were otherwise unremarkable. Infectious, autoimmune, endocrine, and neoplastic work-up all proved unrevealing. Our mitochondrial specialist was consulted, and he was started on arginine and CoQ10.

Further questioning revealed a history of consanguinity between the parents. A muscle biopsy, which was performed to evaluate for possible mitochondrial disorder revealed rimmed vacuoles [4]. EMG/NCV revealed a sensorimotor demyelinating polyneuropathy with secondary axonal loss [5]. Whole exome sequencing was sent, which revealed a homozygous mutation in the SERAC1 gene.



4. Modified Trichrome stained muscle biopsy showing rimmed vacoules

His hospital course was complicated by recurrent respiratory failure requiring re-intubation twice, and ultimately the patient underwent tracheostomy and PEG tube placement. By the time of discharge to rehab, the patient was alert, tracking, had a receptive aphasia, and exhibited anti-gravity movement in all extremities.

Discussion

Our case illustrates a previously undescribed phenotype of SERAC1 deficiency, with demyelinating sensorimotor polyneuropathy and no basal ganglia involvement. While most patients often present early-on with symptoms such as developmental delay, spasticity, and hearing loss, our patient was instead a relatively healthy, functioning young male who presented with recurrent episodes of fever, encephalopathy, and weakness, and had gone previously undiagnosed.

Motor Nerve Conduction:

Nerve and Site	Lat ms	Amp mV	Segment	Dist mm	Lat Diff ms	CV m/s
Median.R to Abductor pollicis brevis (C8-T1).R						
Wrist	4.7	3.1	Abductor pollicis brevis (C8-T1)-Wrist	70	4.7	
Elbow	11.7	2.5	Wrist-Elbow	265	7.0	38
Ulnar.R to Abductor digiti minimi m. (C8-T1).R						
Wrist	3.3	13.2	Abductor digiti minimi m. (C8-T1)-Wrist	70	3.3	
Below elbow	9.9	11.2	Wrist-Below elbow	270	6.6	41
Above elbow	11.9	10.2	Below elbow-Above elbow	100	2.0	50
Peroneal.R to Extensor digitorum brevis (L4-S1).R						
Ankle	5.6	3.5	Extensor digitorum brevis (L4-S1)-Ankle	90	5.6	
Fibula (head)	19.4	2.7	Ankle-Fibula (head)	360	13.8	26
Popliteal fossa	22.2	2.7	Fibula (head)-Popliteal fossa	75	2.8	27
Tibial.R to Abductor hallucis (S1-S2).R						
Ankle	5.9	3.8	Abductor hallucis (S1-S2)-Ankle	90	5.9	

Sensory and Mixed Nerve Conduction:

Nerve and Site	Onset Lat ms	Peak Lat ms	Amp µV	Segment	Dist mm	CV m/s
Median.R to Digit II (index finger).R						
Wrist	2.9	3.8	38	Wrist-Digit II (index finger)	130	45
Ulnar.R to Digit V (little finger).R						
Wrist	2.4	3.4	31	Digit V (little finger)-Wrist	110	45
Radial.R to Anatomical snuff box.R						
Forearm	2.0	2.7	29	Anatomical snuff box-Forearm	100	50
Sural.R to Ankle.R						
Lower leg	4.4	5.6	11	Ankle-Lower leg	140	32
Lower leg	3.3	4.2	9	Ankle-Lower leg	100	30

Needle EMG Examination:

Muscle	Insertion Activity	Spontaneous Activity				Volitional MUAPs					
		Fibs	PSW	Fasc	Other	Poly	Amp	Dur	Rate	Pattern	Effort
Tibialis anterior (L4-L5).R	Increased	2+	2+	0		Few	Normal	Normal	Normal	Normal	Normal
Gastrocnemius.R	Increased	1+	2+	0		Few	Normal	Normal	Normal	Normal	Normal
Vastus lateralis (L2-L4).R	Increased	1+	3+	0		Few	Sl Incr	Sl Incr	Incr	Min Red	Normal
1st dorsal interosseous (C7-T1).R	Increased	1+	1+	0		Few	Normal	Sl Incr	Normal	Min Red	Normal
Biceps brachii (C5-C6).R	Increased	1+	2+	0		Few	Normal	Normal	Normal	Normal	Normal

5. EMG/NCV studies showing a sensorimotor demyelinating polyneuropathy with secondary axonal loss

References

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