International Journal of Medical Ophthalmology

E-ISSN: 2663-8274
P-ISSN: 2663-8266
www.ophthalmoljournal.com
IJMO 2020; 2(2): 11-14
Received: 06-05-2020
Accepted: 10-06-2020

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A case study on SLc25a46 deficiency and its unusual association with hashimoto's thyroiditis: A review of literature

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DOI: https://doi.org/10.33545/26638266.2020.v2.i2a.33

Abstract
Background: SLC25A46, mitochondrial protein shown to be involved in mitochondrial dynamics. Mutation in this protein has been associated with neurological disease.
Case Description: We describe a 19year male presented with decreased vision in both eyes at the age of 5-7years associated with clumpsiness in doing things with upper limb with involuntary movements during rest and tremors.
He had low visual acuity for both distant and near, abnormal color vision in both eyes. Features of bilateral optic atrophy and absent P_{100} waves on VEP. Deranged lipid profile and Raised TSH and TPO antibodies were seen.
Muscle biopsy showed neurogenic atrophy and loss of myelination. Lumbar lardosis was noted and Whole exome sequence analysis homozygous pathogenic mutation in SLC25A46 (C.1018>T/P. Arg 340cys).
Conclusion: It's important to be aware of genetic inheritance and phenotype variants of these mitochondrial disorders. We present a novel variant (p.Arg340Cys) of SLC25A46 deficiency and unusual association with hashimoto's thyroiditis.

Keywords: Optic atrophy; mitochondrial enzyme; hashimoto's thyroiditis; neurological disease; visual evoked potential

Introduction
Mitochondria are the most important cellular organelles for energy production. They produce nearly 90% of the neuronal ADP required for maintenance of neuronal morphology and specialized functions such as synaptic transmission and excitability [1]. Thus mitochondrial dynamics play a vital role in maintenance of neuronal homeostasis and survival.
There are wide variety of proteins that regulate mitochondrial cristae biogenesis, with the master regulators being optic atrophy 1 (OPA1) and the mitochondrial contact site (MICOS) [2]. Most of these proteins involved in mitochondrial dynamics are nuclear-encoded genes causing monogenic disorders such as Charcot Marie tooth disease type2A and autosomal dominant optic atrophy. Studies have shown that this mitochondrial dynamics contribute to both sporadic and familial neurodegenerative disease such as Alzheimer's and parkinsonism [3].
SLC25A46 is a mitochondrial outer membrane protein that was shown recently to be involved in mitochondrial dynamics, either playing a role in mitochondrial fission or regulates oligomerization of mitofusin (MFN) 1/2 [4, 5].
It is characterized by presence of 100 amino acids in three tandem repeats [6]. High levels of these proteins have been found in hindbrain, spinal cord, fornix, corpus callosum, optic chiasma, midbrain and cerebellum [7].
Disease caused by recessive mutations present with phenotypic features such as peripheral neuropathy, early onset optic atrophy, cerebellar degeneration and Ponto cerebellar hypoplasia with variable age of onset and severity [8, 9].
In this study we describe the typical phenotypical and genotypical features of a patient who presented with SLC25A46 deficiency and we implicate an incidental or unusual association with hashimoto's thyroiditis.

Case report

The present work was conducted at Department of Ophthalmology, Vydehi Institute of Medical Sciences And Research Center Bangalore. Patient is a 19year old male patient of south Indian descent born to a second degree consanguineous marriage. An informed consent was taken prior to the study. Clinical study: 19 year old male patient who was apparently normal till 6years of age with normal developmental milestones and same compared to his elder sibling. Presented with decreased vision in both eyes at the age of 5-7years associated with clumpsiness in doing things with upper limb. He developed progressive gait imbalance at the age of 8-10years.

Decreased vision in both eyes was insidious in onset, progressive in nature. No history of diplopia. He had clumpsiness in doing things with upper limb associated with involuntary movements during rest and tremors worsening on lifting objects and has tendency to drop off objects.

The progressive gait imbalance had a onset at 8-10years of age which was gradual in onset, progressive with difficulty in walking in narrow passages, difficulty in lifting foot, walking in the night and self-infliction of injuries with toes and foot. He also had difficulty in getting up from getting up form squatting position and from sitting to supine in early mornings. Wash basin sign (Sensory ataxia): Positive-Worsening of ataxia on eyes closed

Personal history: No bladder complaints.

Bowel control attained by ~14years of age

General physical examination

Hypothyroid facies: Subject was detected with hypothyroidism secondary to hashimoto's thyroiditis.

Absent secondary sexual characters

Stunted growth High arched foot

Ocular examination

Visual acuity:

At the onset: 6/36 both eyes

Presently: Counting fingers at 3metres both eyes

Color vision: Both eyes red green desaturation

Ocular examination:

Head posture: Normal

Facial symmetry: Normal

Adnexa: Normal

Extra ocular movements: Normal

Cover –uncover test: 15degress intermittent exotropia (Right eye dominant)

Nystagmoid movements: Not a pure form of nystagmus. These are slow involuntary eye movements.

Fundus: Both eyes showed evidence of optic Atrophy (Figure A&B)

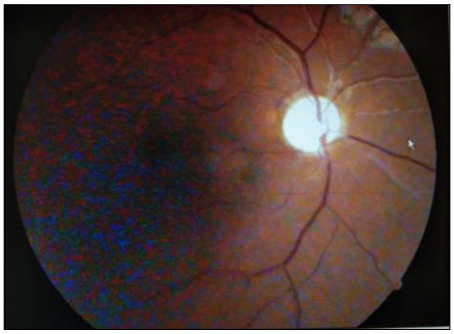

Fig 1: A (Fundus)

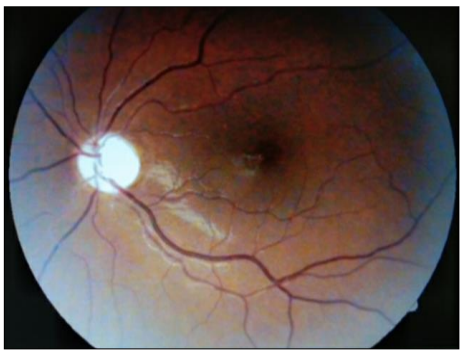

Fig 2: B (Fundus)

Examination of central nervous system

1. Higher mental functions: Normal
2. Other cranial nerves: III, IV, V, VI, VII normal VIII: Bilateral sensorineural hearing loss IX, X, XI, XII normal.
3. **Motor System:** Decreased tone in both upper and lower limbs
   - Power 5/5-Upper limbs 4/5-Lower limb
   - Reflexes biceps, supinator: Brisk
   - Knee jerk: Brisk in both limbs
   - Ankle jerk: Brisk
4. **Sensory Examination:** Pain and temperature sense: Normal
   - Impaired vibration sense and joint position due to involvement of posterior column
5. **Cerebellar Examination:** Broad based, unsteady gait
   - Romberg's sign positive
   - Heel-knee test: Positive
   - Finger nose incoordination

Investigations

- Deranged lipid profile (Raised LDL Levels)
- Vitamin B12:162↓
- Normal liver function test

Thyroid profile

Before therapy:

T3:0.55ng/ml

T4:0.95µg/dl

TSH: >100.00µIu/ml↑↑

TPO antibodies positive>1171.01U/ml↑

Present

T3:1.88ng/ml

T4:6.35µg/dl

TSH: 31.52 µIu/ml

Lactate levels: 9.70mg/dl↑

Pyruvate: 0.99mg/dl Normal

Muscle biopsy

Of Peroneus brevis: Shows neurogenic atrophy and axonal neuropathy of superificial peroneal nerve

On paraffin sections:

HE: Preserved architecture of fibres.Small groups of angulated atrophic fibres seen

MGT: Normal

SDH-Oxidative enzyme: No ragged blue fibres. Type I &Type II group of atrophic nerve fibres

ATPase: Type II group of small atrophic nerve fibres

No COX deficient fibres.
Kpal stain for myelin showed uniform loss of myelinated nerve fibres with few regenerating clusters.

Radiology
MRI-Brain (Philips Achieva 1.5Tesla MR Scanner Saggital T1 FSE, Coronal & axial T2W TSE, FLAIR & DWI) Normal cerebral ventricles; Intracranial tension normal
No detectable lesion

MRI-Spine (Philips Achieva 1.5Tesla MR Scanner)
- Cervical spine: Loss of lardosis
- Thoracic spine: Unremarkable
- Lumbar spine: Loss of lardosis; Mild disc bulge of L4-5 and L5-S1indenting the thecal sac
- Knee and hand radiographs normal

Molecular analysis: Whole exome sequence analysis was performed. Analysis showed a homozygous pathogenic mutation in SLC25A46 (C.1018>T/P.Arg 340cys)
Carriers are mother and other family members (C.1018>T)

VEP: P_{100} wave forms were absent. (Figure C&D)
Suggestive of anterior visual pathway defect.

Right Eye

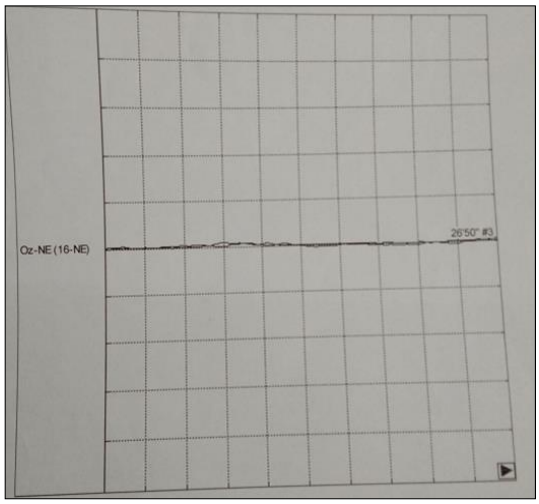

Fig 3: C (Vep right eye)

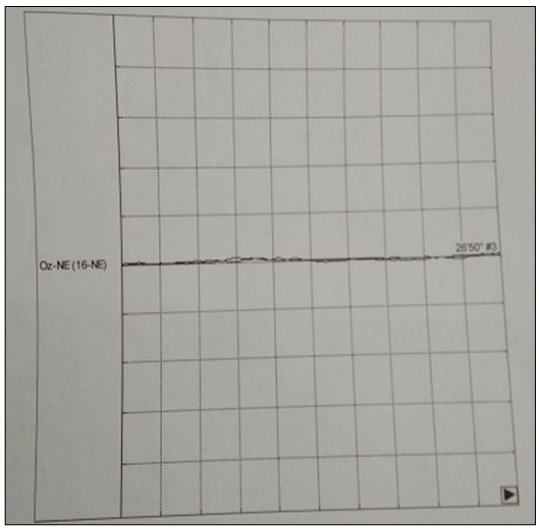

Fig 4: D: VEP (Left eye)

Discussion
SLC25A46 plays a critical role in mitochondrial dynamics and the maintenance of mitochondrial cristae, which are particularly important in neurodevelopment and neurodegeneration.
It consists of 6transmembrane helices that form an aqueous pore and highly conserved consensus sequence. Mutation of p.Arg340Cys are located on the loops of repeat sequence facing inside of matrix space. It is located between TM5 and TM6.As per the NCBI database arginine at position 340 is a conserved component in mitochondrial family. And this SLC25A46 is essential for growth and development of neuronal processes [10].
SLC25A46 mutations and their association with neurological disease were first reported in 2015, more than 28 patients with various mutations from 16 unrelated families have been diagnosed genetically. Of these, 50% of missense mutations; 16.7% of nonsense mutations; 11.1% of splice variants; and 22.2% were micro-deletions, insertions and duplications [11].
Mutation in this component has been widely associated with childhood onset symptoms, optic atrophy, cerebellar or sensory ataxia, speech difficulties and wasting of lower limbs [4]. In our study patient presented with typical features of p.Arg340Cys mutation. Hearing loss is a common finding and it relates with the mutation in skeletal muscle load and its progression depends on burden of mutated DNA in cochlea [12].
Endocrinal pathology in a mitochondrial disorder is a common association.
But in our present study association of hashimoto's thyroiditis is an unusual or an incidental finding, It's association with mitochondrial dysfunction is yet to be proved in literature.
In our study we report a novel variant (p.Arg340Cys) in SLC25A46 and have implicated an unusual association of mitochondrial dysfunction with hashimoto's thyroiditis.

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