

Common and Unusual Presentations of *SUCLA2* Gene Mutations require thorough Diagnostic Work-up

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Received Date: 08 September, 2018; Accepted Date: 20 September, 2018; Published Date: 20 September, 2018

Letter to the Editor

In a recent, interesting article, Güngör et al. reported about a 25 months-old male with Mitochondrial Depletion Syndrome (MDS) due to a novel mutation in the Succinate-CoA-ligase ADP-forming, beta-subunit (*SUCLA2*) gene [1]. Mutations in this gene result in succinate-CoA-ligase deficiency, a disorder of the mitochondrial tricarboxylic acid cycle [2]. Phenotypically the patient presented with encephalomyopathy, manifesting as microcephaly, basal-ganglia lesions, dystonia, absence of head and truncal control, failure to thrive, sensorineural hearing loss, quadraparesis, and scoliosis [1]. We have the following comments and concerns.

MDS is not only due to mutations in the *POLG*, *TK2*, *DGUOK*, *SUCLA2*, *SUCLG1*, *PEO1*, *MPV17*, and *RRM2B* genes but also due to mutations in the Thymidine-phosphorylase (*TYMP*) gene [3]. *TYMP* mutations manifest as Mitochondrial Neuro-Gastro-intestinal Encephalo-myopathy (MNGIE), which is potentially treatable [3].

The authors describe the phenotype as encephalo-myopathic [1] but the patient had quadraparesis, and there is no mentioning that Needle-electromyography (EMG) was myopathic, or that muscle biopsy was myopathic [1]. Thus, we should be informed if Creatine-kinase (CK) or lactate was elevated, and if the patient underwent needle-EMG or muscle biopsy. Since the activity of respiratory-chain complexes may be reduced on biochemical investigations of the muscle homogenate in *SUCLA2* mutation carriers [4], we should know if the patient underwent investigations of the respiratory chain activity on muscle biopsy or skin fibroblasts [Figure 1]. Muscle hypotonia may go along with myopathy but can be due to affection of the brainstem or the basal ganglia as well [5]. Muscle wasting not necessarily reflects myo-

pathy or neuropathy since it can be attributed to inactivity from a non-neuromuscular cause as well.

Since patients carrying *SUCLA2* mutations have been described to develop epilepsy with infantile spasms or general convulsions with onset between birth and age 3 years [6], it is crucial to know if the history was positive for seizures, if paroxysmal activity was recorded on EEG, and if the patient underwent provocation EEG, or video-EEG monitoring.

We should be informed if the patient presented with generalised, regional, or focal dystonia, if the respiratory muscles were affected, and how the patient was managed with regard to feeding, spasticity, muscle weakness, wasting, scoliosis, and dystonia. Spasticity and dystonia may respond to pharmacotherapy or botulinum toxin. Scoliosis or camptocormia may require surgical stabilisation of the spinal column. Monitoring the involvement of respiratory muscles requires blood-gas-analysis for nocturnal oxygen saturation.

Since microcephaly is not a typical phenotypic feature of *SUCLA2* mutations, an explanation for this unusual presentation should be provided, particularly if microcephaly resulted from a double trouble. Since microcephaly is a common feature of chromosomal defects, we should be informed if cytogenetic studies for chromosomal aberrations were carried out, and if consanguinity was truly excluded since the parents originated from the same town [1]. In this respect it is essential to investigate both parents neurologically, to carry out routine blood tests, and to find out if the grandparents or the siblings of the patient presented with any neurological abnormality.

We should be informed about follow-up investigations and the outcome of this patient. Of particular interest is to know the clinical course between the first investigation at age 2 years and the

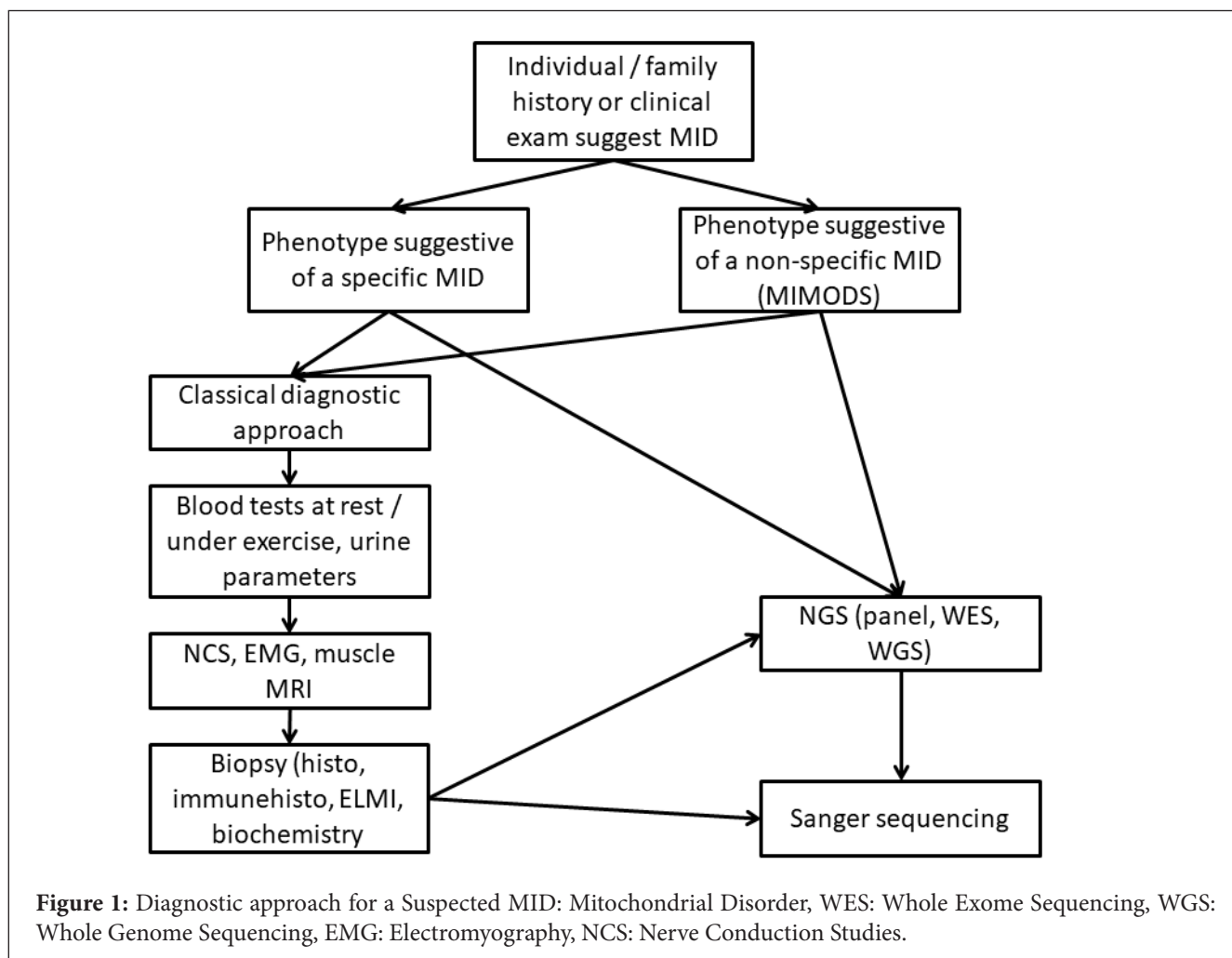
cerebral MRI at age 7 years, if the patient required ventilatory support, if the patient required tube feeding, if he had to undergo implantation of a Percutaneous Endoscopic Gastrostomy (PEG), if he developed seizures during these five years, and if the EEG remained normal at all follow-up investigations.

Overall, this interesting case could profit from a more detailed description of the phenotype, from presentation of follow-up data, and clinical examination of first-degree relatives of the index case. Since the clinical presentation was at variance in some points compared with previously *SUCLA2* cases, a double trouble needs to be excluded. Generally, diagnostic work for suspected *SUCLA2* mutations should include the history, clinical exam, nerve conduction studies and EMG, cerebral imaging, cardiac investigations, and a muscle biopsy, in case no genetic work-up is feasible [Figure 1]. A more modern approach will be genetic investigations by a panel or Whole Exom Sequencing (WES) [Figure 1].

There are no conflicts of interest.

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