

# Phenotypic and genotypic peculiarities in Chinese patients with Leigh syndrome

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*To the Editor:* With interest we read the article by Yu *et al*<sup>[1]</sup> about a retrospective study of 13 pediatric patients with Leigh syndrome from a single center in China collected over a period of 17 years. The authors concluded that patients with ophthalmoplegia, muscle weakness, ataxia, and respiratory insufficiency should be screened for mutations in genes located on the mtDNA.<sup>[1]</sup> Patients with suspected Leigh syndrome are recommended to undergo determination of cerebrospinal fluid (CSF) lactate and cerebral imaging.<sup>[1]</sup> We have the following comment and concerns.

The main shortcoming of the study is that it was retrospective. The retrospective design implies that certain investigations were not carried out in each patient with the result that the findings are only partially representative of Leigh syndrome. A retrospective design has the disadvantage that conclusions about the frequency of certain phenotypic features are not reliable. This shortcoming lastly allows drawing only conclusions with strong limitations.

A further shortcoming of the study is that no follow-up data were provided. Thus, the data represent only a cross-sectional perspective of the cohort. The study may produce completely different results if the investigations would be repeated a few years later. Since mitochondrial disorders (MIDs) are progressive in nature, it is crucial to know the full-blown end-stage of a phenotype. Otherwise conclusions about the phenotypic expression, prognosis, and outcome are not reliable.

Another shortcoming of the study is that first degree family members were not investigated. Thus, we do not know if the mutations were inherited from the mother's side or occurred sporadically. Since about 75% of the mtDNA mutations are hereditary and transmitted via the maternal line,<sup>[2]</sup> we should know in how many of the cases the mother of an index case carried the mutation and with which heteroplasmy rate, and if she manifested clinically or

not. Knowing the way of transmission is crucial for genetic counselling of all potential carriers of the mutation.

Missing is also information about the presence or absence of stroke-like episodes (SLEs) in the cohort. Since SLEs were reported in single patients with Leigh syndrome,<sup>[3]</sup> we should be informed if any of the 13 included patients had a history of SLEs or if imaging in any of the 13 patients was indicative of a stroke-like lesion (SLL), the morphological equivalent of a SLE. Particularly in patient 1 the history should be positive for a SLE since he carried the m.3243A>G variant in the *MT-TK* gene, which is responsible for MELAS in 80% of the cases. On the other hand, about 70% of the MELAS patients develop at least one SLE during the disease course. Thus, it is conceivable that this patient had a history of a SLE.

Interestingly, patient No. 7 had left ventricular hypertrabeculation (LVHT), also known as noncompaction.<sup>[1]</sup> This finding should be stressed since it is one of the few patients with Leigh syndrome who manifested cardiologically with LVHT. Since LVHT patients carry the risk of developing ventricular arrhythmias, cardio-embolism, heart failure, or sudden cardiac death, these patients require particular cardiologic surveillance, not to miss the point at which appropriate diagnostic and therapeutic measures are indicated. Accordingly, we should be informed about the outcome of patient No. 7, particularly if he developed any of the above mentioned complications associated with LVHT and if he required cardiac treatment. Since LVHT may occur in other family members as well,<sup>[4]</sup> we should know if they were seen by a cardiologist.

Unusual compared to previous findings is that none of the patients with Leigh syndrome in the investigating center carried a mutation in a nDNA located gene. Since MIDs in pediatric patients are more likely due to mutations in nDNA located genes, and MIDs in adults more likely carry

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mutations in mtDNA located genes, we can expect nDNA related Leigh syndrome at least in some patients of the cohort. Unusual is also the absence of epilepsy in all 13 patients. In most other cohort studies of patients with Leigh syndrome epilepsy is a prominent feature of the phenotype. Is the phenomenon due to a special diet the included patients were taking or is it due to application of a specific treatment, such as antioxidants, vitamins, or cofactors? Thus, it is crucial to know about the current medication each of the included patients was taking.

We disagree with the notion that elevated CSF lactate and elevated CSF protein are specific markers for the diagnosis of Leigh syndrome. Elevated CSF lactate and protein is a non-specific finding in a number of different MIDs. Already in Kearns-Sayre syndrome and MELAS syndrome elevated protein respectively elevated lactate are included in the diagnostic criteria. Thus, these parameters are of limited value for diagnosing Leigh syndrome.<sup>[5]</sup> The main criteria for diagnosing Leigh syndrome are the presence of symmetric subcortical brain lesion and phenotypic features compatible with a MID.

Overall, this interesting cohort study of 13 patients with Leigh syndrome could be more meaningful if a prospective design would have been applied, if more information about the family history, the mode of transmission, and

follow-up data would have been provided. The absence of epilepsy and the absence of mutations in nDNA located genes needs to be discussed.

### Conflicts of interest

None.

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## Reply to “Phenotypic and Genotypic Peculiarities in Chinese Patients with Leigh Syndrome”

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*To the Editor:* We really appreciate the readers' interest and comments about our article, and to have the opportunity to make an explanation.<sup>[1]</sup>

The phenotype and genotype characteristics of 13 Chinese Leigh Syndrome (LS) patients were retrospectively reported in our paper, and we acknowledge certain investigations were not carried out in each patient, for instance, organic acids and amino acids analysis in urinary and blood, and magnetic resonance spectroscopy scanning. However, patients' clinical features, brain magnetic resonance imaging, and genotypic analysis were all included in our study, which was consistent with the diagnosis of LS.<sup>[2]</sup> The data about patients' phenotypic features was reliable. This retrospective study had a long time span. Follow-up for each patient was difficult, and most of the participants were lost to follow-up. Thus, we only provide a cross-sectional study. But it was certain that 3 patients died from respiratory failure 3 months, 6 months and 6 years later respectively after diagnosis.

We agree with the comment of the readers that knowing the way of transmission is crucial for genetic counseling. Unfortunately, some patients' mothers and other relatives refused to provide specimen for genotype analysis. The available data showed 7 clinically asymptomatic mothers of the index cases carried the mutations but the exact heteroplasmy rates were not all available; besides, the mutation in patient No.7 was *de novo*.

Stroke-like episodes (SLEs) were absent in our cross-sectional study, and no patient had brain imaging indicating a stroke-like lesion (SLL). Patient No.1 indeed carried the m.3243A>G mutation, but he was not consistent with the diagnosis of mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes/Leigh (MELAS/LS) overlap syndrome. He didn't present SLEs, such as headache, seizure, hemiplegia, cortical

blindness or hemianopsia, nor his brain imaging showing SLL. The m.3243A>G mutation in MTTL1 gene could present different clinical phenotype without SLE or SLL.<sup>[3,4]</sup>

In our article, we mentioned patient No. 7 suffered from left ventricular noncompaction and preexcitation syndrome. Holter monitor of the patient in our hospital demonstrated sinus arrhythmia and intermittent preexcitation syndrome. The ejection fraction of his left ventricle was normal. He was treated with coenzyme Q10, L-carnitine, thiamine, riboflavin, etc. No special therapy was given after consultation with a cardiologist. The DNA sample derived from maternal blood did not reveal the m.13513G>A mutation, suggesting a sporadic mtDNA mutation in the index case. The other family members didn't go to see a cardiologist. After 1 year follow-up, the patient's condition was stable without heart failure, or cardio-embolism.

According to the diagnostic criteria proposed by Baertling *et al*,<sup>[2]</sup> there were 12 patients with clinical features and brain lesions meeting the diagnosis of Leigh-like syndrome in our center, except the 13 reported mtDNA mutation cases. After the entire mitochondrial genome and exome sequencing, 1 patient was diagnosed with biotin-responsive basal ganglia disease, and two patients had variants of undetermined significance in nDNA located genes related to LS, while the other 9 patients had no confirmed genetic variants associated with other diseases. Seizure was absent in our patients during our investigation. LS is characterized by bilateral symmetrical lesions in the brainstem and basal ganglia pathologically with gliosis, vacuolation, capillary proliferation, relative neuronal preservation, and severe ATP depletion, reactive oxygen species, hyperlacticacidemia and excitotoxicity might contribute to the neuropathogenesis.<sup>[5]</sup> The presence of seizure may be associated with the range of lesions involvement and the extent of gliosis, excitotoxicity, etc. In addition, this was a cross-sectional study and the sample size was relatively small.

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Seizures maybe occur during the disease progression. The participants didn't take a special diet or a specific treatment.

We didn't mean to make the notion that elevated CSF lactate and protein were specific markers for the diagnosis of LS. In the criteria for LS proposed by Rahman *et al*<sup>[6]</sup> in 1996, high lactate levels in blood and/or cerebrospinal fluid (CSF) was included. The requirement for lactate levels has been eliminated for the normal blood and/or CSF lactate levels in some patients. However, in our cohort, we found all the 6 patients with lumbar puncture had elevated lactate levels in CSF (6/6). The positive rate of elevated lactic acid in CSF seemed to be higher than that in blood. The elevated CSF protein was already included in the diagnostic criteria for Kearns-Sayre syndrome (KSS). We thought the elevated lactate and protein level of CSF was helpful for LS diagnosis different from other non-mitochondrial encephalopathy, such as neuromyelitis optica spectrum disorder (NMOSD).

We presented the phenotypes and mtDNA mutations of the LS patients in our center, which was a single center retrospective study with a small sample size. There were many limitations. We appreciate the comments and advices again, and hope to design a prospective study with more participants, nDNA genotypes analysis and follow-up data, which would validate and expand our findings.

### Conflicts of interest

None.

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