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Original Article

Clinical features of mitochondrial encephalomyopathies in China: 97 case study and literature review

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Abstract: Objective: To comprehensively investigate the mitochondrial encephalomyopathies in China for better diagnosis and treatment. Methods: A total of 97 cases from the PLA General Hospital between January 1993 and September 2012, and 815 cases reported from Wanfang Database, the Chinese National Knowledge Information database, Chinese Biology and Medicine Library Database up to September 2012, were reviewed and analyzed. The information analyzed included general conditions, the first symptom, the way of onset, clinical manifestations, findings from physical examinations, imaging examinations, muscle biopsy and genetic testing. Results: A total 912 cases were identified with a male-to-female ratio of 1.66:1. The age of patients ranged from 56 days to 78 years with a median age of 19 years. The most common type was mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) (50.3%). They frequently reported headaches (46.3%) and presented with an A3243G mitochondrial DNA (mtDNA) mutation (84.3%). Other mitochondrial encephalomyopathies included Leber's hereditary optic neuroretinopathy with decreased vision (95%) and a G11778A mtDNA mutation (42.6%), chronic progressive external ophthalmoplegia with ptosis (76.2%) and ocular movement disorder (79.2%), Leigh syndrome with delayed development (29.2%) and symmetrical abnormalities in the brainstem and basal ganglia (98.2%), myoclonic epilepsy and ragged red fiber with convulsions (35.7%). Many patients had elevated levels of lactic acid, and most showed myogenic injury in the electromyography signals. In the Kearns-Sayre syndrome patients 76.7% showed heart block in the electrocardiograms. Conclusions: Nearly all types of reported mitochondrial encephalomyopathies are present in Chinese population. If the clinical course, neurological findings and imaging features are suggestive of mitochondrial encephalomyopathies, DNA testing may be used for confirmation. If the results are not conclusive, then a muscle biopsy should be performed.

Keywords: Mitochondrial encephalomyopathy, MELAS, MERRF, leigh syndrome, CPEO, LHON

Introduction

Mitochondria are the main organelles to produce energy for cellular activities through oxidative phosphorylation. They contain various respiratory chain enzymes involved in the biochemical reactions of aerobic metabolism [1, 2]. Most of these enzymes are encoded by nuclear genes that are transmitted in the Mendelian inheritance [3, 4]. Complexes (I-V) in the electron transport chain are embedded in the inner membrane, and complex II is composed of only nuclear DNA (nDNA)-encoded subunits, whereas the other complexes contain both nDNA- and mitochondrial DNA (mtDNA)-encoded subunits. In addition, the mtDNA also encodes 2 rRNA and 22 tRNA. Defects in these genes in the mtDNA are transmitted in the maternal inheritance [5, 6]. The disruption of these genes will have an impact upon the function of organs, especially those that are highly dependent on aerobic metabolism, such as the brain and muscles (cardiac and skeletal muscles), and cause a heterogeneous group of diseases called mitochondrial encephalomyopathies.

Mitochondrial encephalomyopathies is a disease system discovered in the past 50 years [7]. In 1958, Kearns and Saire reported a case of KSS characterized by extraocular muscle paralysis, retinitis pigmentosa and cardiac block [8]. In 1962, Luft first reported a case of mitochondrial myopathy, which was biochemi-

cally confirmed to be caused by oxidative phosphorylation decoupling [9]. In 1980, Fukuhara reported a case of myoclonic epilepsy with broken red fibers (MERRF) [10]. In 1983, Johnson proposed chronic progressive external muscle paralysis (CPEO) [11]. In 1984, Pavlakis reported the first case of mitochondrial encephalomyopathy with Lactatemia and stroke-like seizures [12].

The global birth rate of mitochondrial diseases is 1/5000 [4], while the incidence of mitochondrial encephalomyopathy is different in the literature [13]. The initial symptoms vary considerably, ranging from motor intolerance to stroke-like attacks. The clinical manifestations of different types of mitochondrial encephalomyopathy are also different with different duration. The prognosis is usually poor. 80% of the patients have elevated blood lactic acid level, 60% of the patients have myogenic lesions based on electromyography. Imaging findings include white matter encephalopathy, basal ganglia calcification or brain atrophy. Blood DNA analysis and muscle biopsy are often used to confirm the diagnosis [14, 15]. At present, there is no specifically effective treatment for the disease [16].

To better understand the occurrence and features of the diseases in China, we retrospectively analyzed the cases from our hospital and reported in literature up to September 30, 2012. The findings will help better diagnosis and management of the disease, not only for Chinese population, but also for other populations as well.

Methods

Literature search strategy

The Wanfang database, Chinese Medical Journal Database (CMJD), Chinese Biology and Medicine Library Database and Chinese National Knowledge Information Database were searched for studies published up to September 30, 2012. The search used Chinese term mitochondrial encephalomyopathy and other related names for the disease. Studies were included if they reported clinically suspected or confirmed mitochondrial encephalomyopathies. Suspected cases were based on acceptable clinical presentations. Confirmed cases were those not only having clinical presentations but also having at least one of the following: (1) characteristic changes in muscle biopsy, such as ragged red fibres (RRF) on Gomori trichrome stain (GMT), or decreased succinate dehydrogenase (SDH) or cytochrome C oxidase (COX) staining; (2) evidence of mutations or deletions in mtDNA; (3) deficiency of respiratory chain enzymes or pyruvate utilization enzymes in muscle; (4) evidence of abundant and abnormal mitochondria by electron microscopy; (5) findings in brain biopsy with a) individually mineralized neurons in the thalamus, hypothalamus and sometimes in the basal ganglia (i.e. neuronal calcinosis), b) white matter gliosis, particularly in the brainstem and cerebellum, c) dysmyelination or demyelination of white matter in the cerebral hemispheres, d) focal dysplasias and neuronal loss in the inferior olivary, red and dentate nuclei and the cerebellar cortex, e) periventricular necrosis or spongiform changes in Leigh encephalopathy [9, 17]; (6) a family member with a proven mitochondrial disease. Studies were excluded if no sufficient data were presented.

Subjects

In addition, a total of 97 cases were analyzed from our hospital up to September 30, 2012. They were included based on the same inclusion and exclusion criteria as for the literature search.

Statistical analysis

All data were processed using Microsoft Excel 2000 and expressed as number or percentage.

Results

Overview of mitochondrial encephalomyopathies in China

Our literature search resulted in a total of 368 studies in the first round of screening. After reviewing their titles and abstracts, 350 papers were further examined for exclusion and inclusion criteria. At last, 332 papers were included, of which 32 studies were about Leber's hereditary optic neuroretinopathy (LHON), 38 studies were about Leigh's syndrome, 41 studies were about CPEO, 20 stud-

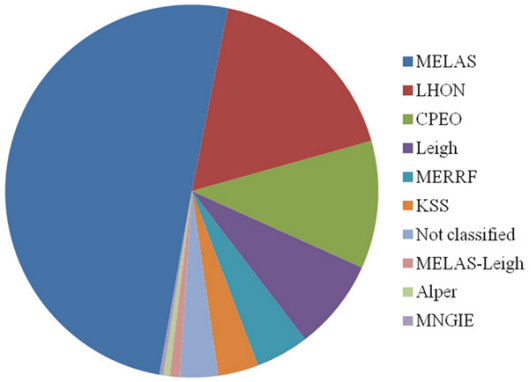

Figure 1. Distribution of mitochondrial encephalomyopathy cases in China.

ies were about the Kearns-Sayre syndrome (KSS), 156 studies were about mitochondrial encephalomyopathy with lactic acidosis and stroke-like (MELAS), 21 studies were about myoclonic epilepsy and ragged red fibers (MERRF), two studies were about mitochondrial neurogastrointestinal encephalomyopathy (MNGIE), four studies were about MELAS-Leigh, two studies were about Alpers and 16 studies could not be classified. A total of 815 cases were analyzed from the literature. In addition, a total of 97 cases were obtained from our hospital. This distribution of mitochondrial encephalomyopathies is presented in **Figure 1**. The most common one were MELAS (50.3%) followed by LHON (17.5%), CPEO (11.1%), Leigh (7.89%). MERRF (4.61%), KSS (3.51%), unclassified type (3.29%), MELAS-Leigh (0.88%), Alpers (0.55%) and MNGIE (0.33%) were all less than 5%. Of the 912 cases, only one did not report the gender, 61 cases did not report the age. Therefore, the ratio of male/female of the patients was 568:343, the ages ranged from 56 d to 78 years, the ratio of suspected cases/confirmed cases was 116:796.

MELAS

Since described initially almost 25 years ago [18], MELAS has been expanded to include overlapping syndromes. A total of 459 cases were identified, the ratio of male and female was 273:186, the reported ages ranged from 4 m to 65 years, and the median age was 20 years old (**Figure 2**). The onset ages were reported in 376 cases and they ranged from 4 m to 59 years, and the median age was 18 years. The initial symptom were not recorded in 213 cases, while in the remaining cases the initial symptoms included headache (26.4%), followed by convulsions (15.4%), epilepsy (11.8%), limb weakness/fatigue (10.6%), stroke-like episodes (10.2%), visual symptoms (8.94%), hearing loss (5.28%), fever (5.28%), conscious disturbance (2.44%), dizziness (0.81%), vomiting (0.81%), memory loss (0.81%), other disorders (such as disorder of pancreas or kidney) (0.81%), and mental disorder (0.41%) (**Figure 3**; **Table 1**).

Elevated creatase (4.55%) and abnormal cerebrospinal fluids (76.3%), such as elevated lactic acid and protein content, were observed in some patients, and elevated plasma lactic acid (92.7%) was very common. Of 115 patients who conducted electromyography (EMG), 81 were found abnormal (70.7%), 52 had myogenic injury, 16 had neurogenic injury, three had both myogenic injury and neurogenic injury, the remaining had slow nerve conduction. Of 155 patients who conducted electroencephalography (EEG), 141 were found abnormal; most of them displayed spike wave, slow wave or both. However, ECG is usually not definitive in diagnosis of MELAS. 24 of 74 patients showed evidence of cardiomyopathy, pre-excitation or heart block.

Though there was no specific change on computed tomography (CT), we could still find some regularity (**Figure 4**). Of the CT-scanned 182 patients, low density signals in the lobes were found in 44.5% patients, followed by calcification of basal ganglia (28.0%), negative manifestation (20.9%), cerebral infarction (18.7%), brain atrophy (17.6%), high density signals in the cortex/basal ganglia/lobes (2.75%), and white matter demyelination (0.55%). Only four patients received CT angiography. However, one patient was found abnormal, with a smaller distal branch of the left middle cerebral artery than the right artery. Resonance imaging (MRI) was performed on 317 patients, and multiple disease loci on brain images could be seen in **Figure 5**. 76 patients carried out MR angiography, 22.4% had abnormalities and almost all these cases showed abnormal distal branch of the middle cerebral artery. In addition, 14 patients performed digital subtraction arteriography (DSA), two cases were found

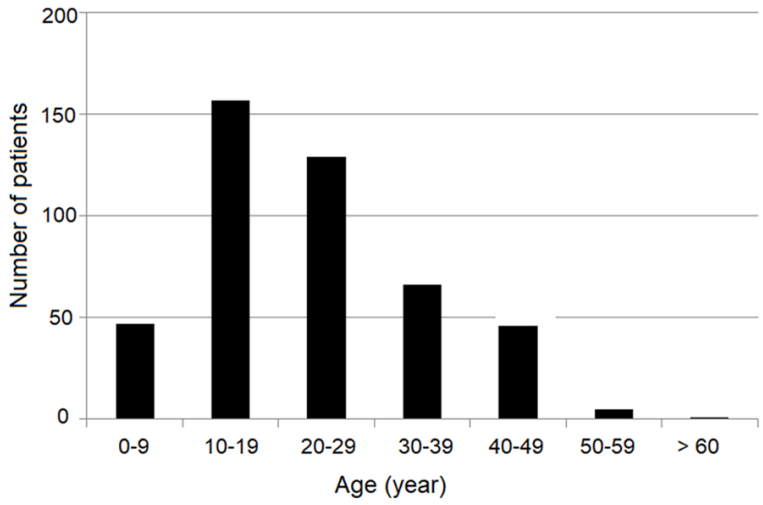

Figure 2. The number of cases at different ages in MELAS patients.

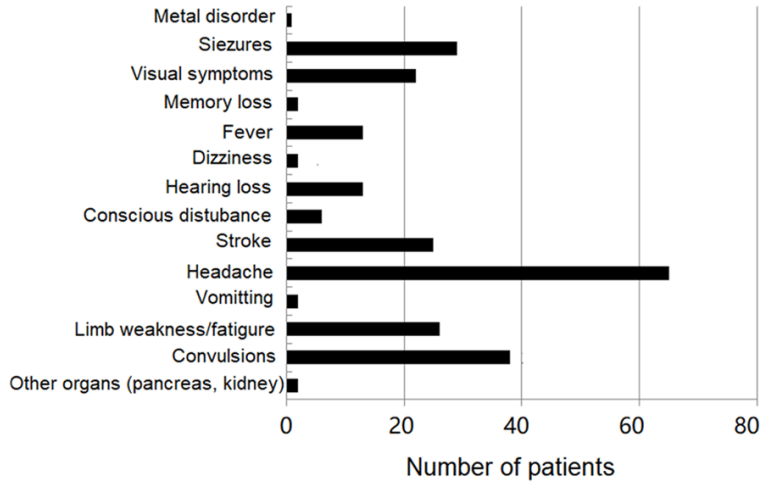

Figure 3. Clinical features of MELAS patients.

abnormal, but there was no valuable information provided for the diagnosis. Biochemical analysis was also reported for the MELAS patients. 42 of 50 MELAS patients had increased lactate and decreased N-acetyl aspartate. Two patients also conducted positron emission tomography (PET), both had radioactively sparse areas in the brain.

A total of 363 cases received muscle biopsy, and 341 cases (93.9%) were identified to be MELAS. 191 cases were DNA-tested for mutation, and 172 were found abnormal. Of which 161 (84.3%) had mtDNA A3243G mutation, seven (3.66%) had mtDNA G13513A mutation, and each of three (0.52%) had mtDNA T3271C, T3271C and T6253C mutations, one (0.52%) had a 276 bp depletion of mtDNA 3314-3589. The remaining 19 cases (9.95%) were negative.

CPEO

A total of 101 CPEO cases were included in our study, only one of them was unknown for gender, and seven patients unknown for age. The ratio of male and female was 47:53,the ages ranged from 9 to 67 years with a median age of 32.5 years (**Figure 6**). The highest proportion of initial symptom was ptosis (75.2%); other symptoms were exercise intolerance, limb weakness, diplopia, ocular movement disorder and decreased vision (**Table 2**). In the course of disease, 79.2% patients were found to have ocular movement disorder. Other symptoms included reduced muscle strength (27.7%), diplopia (14.9%), dysphagia (13.9%), abnormal tendon reflex (7.92%), heart block (6.93%), alalia (5.94%), hearing loss (4.95%), migraine (3.96%), dystonia (3.96%), myatrophy (3.96%), retinitis pigmentosa (3.96%), developmental delay (3.96%), emaciation (3.96%), short stature (2.97%), nystagmus (0.99%), pathological signs (0.99%), and mental retardation (0.99%). 19 (18.8%) patients had family history.

Nine of 20 patients tested were found elevated lactic acid, while 25 of 64 patients were found elevated creatase. All 37 patients who performed neostigmine testing were negative. 52 patients conducted ECG, seven were abnormal, including heart block, abnormal T wave or bearing premature. 28 of 52 patients who performed EMG were abnormal, of which 24 had myogenic injury, four had neurogenic injury. EEG was conducted in three patients; none of

Table 1. Clinical features of individuals with MELAS

Sign/Symptom	Present	Recorded	Percent (%)
Reduced muscle strength [3, 8, 9, 12, 18, 27]	51	263	19.4
Dystonia [3, 8, 9]	25	263	9.51
Pathological signs [3, 8]	52	263	19.8
Abnormal tendon reflex [3, 8]	44	263	16.7
Short stature [3, 8, 18, 25]	102	263	38.8
Disturbance of intelligence [3, 8, 18, 25]	114	263	43.3
Family history [3, 8]	42	263	16.0
Diabetes mellitus history [3]	24	263	9.13
Mental disorder [3, 8, 18]	37	421	8.79
Visual symptoms [3, 8, 18, 25]	62	421	14.7
Headache [3, 8]	195	421	46.3
Convulsions [3, 8]	167	421	39.7
Memory loss [3, 8]	5	421	1.19
Hearing loss [3, 8]	36	421	8.55
Ataxia [3, 8]	22	421	5.23
Stroke [3, 8, 9, 12, 18, 25]	102	421	24.2
Nausea, vomit [3, 8, 9, 12, 18, 25]	69	421	16.4
Seizures [3, 8, 9, 12, 18]	102	421	24.2
Limb weakness [3, 8, 9, 12]	51	421	12.1
Conscious disturbance [3, 8, 9]	37	421	8.79
Fever [3, 8]	52	421	12.4
Cognitive impairment [3, 8]	13	421	3.09

Present = number of individuals demonstrating a clinical feature; Recorded = number of individuals evaluated for each clinical feature.

them was normal, showing spike wave, slow wave or both. CT/MRI examinations were reported in 31 cases. Four were abnormal, showing calcification of basal ganglia, brain atrophy or low density area. Muscle biopsy was performed in 81 patients, and 53 cases were positive. DNA testing was not common and was done only in 11 patients. The results showed that five were normal, four had mtDNA deletion, and two had mtDNA T10909C mutation.

KSS

A total of 32 KSS cases were included, the ratio of male and female was 25:7 and the ages ranged from 5 to 36 years with a median age of 14.5 years. The initial symptoms are shown in **Table 3**. 25 patients had ocular movement disorder, 23 patients had ptosis, 16 patients had pigmentary retinopathy, 15 patients had hearing loss, 14 patients had short stature, nine patients had blurred vision, six patients had diplopia, six patients had mental retardation, five patients had reduced muscle strength, five patients had decreased tendon reflex, thee patients had dystonia, one patient had slow light reflex and two patients had family history.

20 of 22 patients were found to have elevated lactic acid, while eight of nine patients were found to have elevated creatase. ECG is a typical examination for KSS, 23 patients conducted ECG and all of them showed heart block. EEG was conducted in six patients; five of them were abnormal, showing spike wave, slow wave or both. Two of six patients who performed EMG were abnormal, of which one had myogenic injury, the other had neurogenic injury. Four of nine CT-scanned patients were found abnormal, including bilateral calcification of globus pallidus, suprasellar cistern, quadrigeminal cistern or brain atrophy. 17 of 20 patients receiving MRI were abnormal, most of which showed bilateral symmetry long T1 and long T2 signals on the white matter. 27 of 28 cases had positive pathology results. DNA testing showed that 13 cases were abnormal, including four cases of mtDNA deletion and two cases of mtDNA A3243G mutation.

MERRF

Our study contained 42 MERRF patients, the ratio of male and female was 23:19, and the ages ranged from two to 66 years with a median age of 17.5 years. The initial symptoms are shown in **Table 4**. 13 patients had reduced muscle strength, 12 patients had ataxia, seven patients had pathology signs, six patients had abnormal tendon reflex, two patients had dystonia, five patients had dysarthria, five patients had nystagmus, five patients had memory loss and six patients had family history.

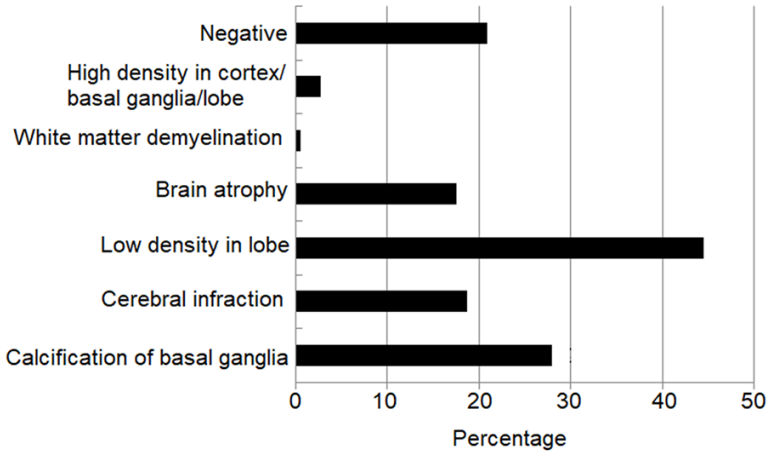

Figure 4. Features of CT scan in 182 MELAS patients.

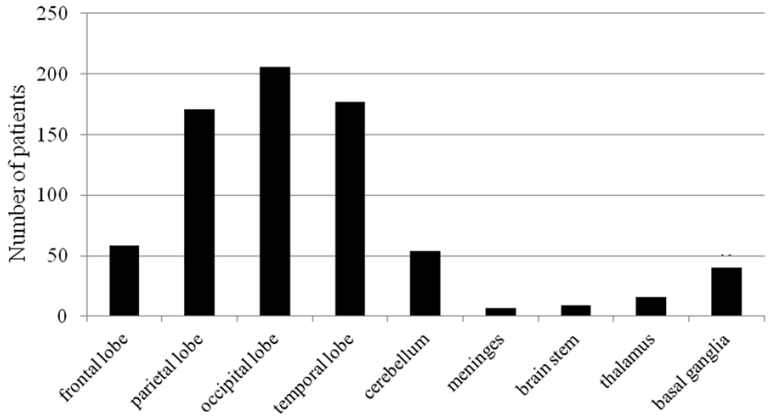

Figure 5. Multiple disease loci on brain images of 317 MELAS patients.

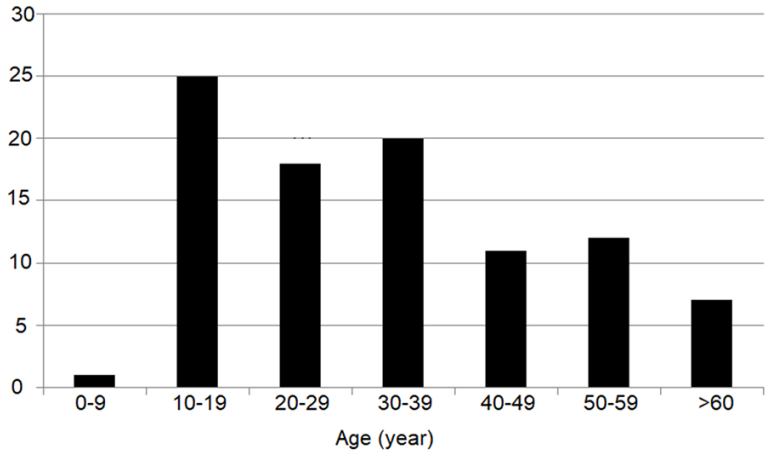

Figure 6. The number of cases of different ages in 94 CPEO patients.

19 of 21 patients were found to have elevated lactic acid, while eight of nine patients tested had elevated creatase. Four patients conducted ECG and two were found abnormal, both of them had heart block. EEG was conducted in 29 patients; 27 of them were abnormal, showing spike wave, slow wave or both. 16 of 18 patients who performed EMG were abnormal, of which seven cases had myogenic injury, eight cases had neurogenic injury, and one case had decreased nerve conduct velocity. ECG is a typical ecamination for MERRF. 23 of 30 who conducted ECG showed heart block. EEG was conducted in six patients; five of them were abnormal, showing spike wave, slow wave or both. Two of six patients who performed EMG were abnormal, of which one had myogenic injury, the other had neurogenic injury. 14 of 21 CT-scanned patients were found abnormal, 22 of 28 MRI-scanned patients were found abnormal, most of which showed cerebral or cerebellar atrophy or calcification of the basal ganglia or white matter, or a combination of the above findings. Only one patient conducted magnetic resonance spectroscopy (MRS) and found to have increased lactate and decreased N-acetyl aspartate. 36 of 40 cases were positive for pathological examinations. DNA testing was conducted in 18 cases, and 13 cases were abnormal, including 6 mtDNA A8344G and 2 mtDNA A3243G mutations.

LEIGH

Leigh syndrome is a neurodegenerative disease that most commonly presents in infancy or childhood. Our study contained 72 LEIGH patients. The ratio of male and female was 45:27, the ages ranged from 56 d to 32 years, with a median age of three years. The initial symptoms are

Table 2. The initial symptoms of CPEO patients

Initial symptom (n=101)	Number of individuals	Percent (%)
Ptosis [3, 8, 27, 33]	77	75.2
Unknown [3, 27, 33]	15	14.9
Exercise intolerance [33]	2	1.98
Limb weakness [8, 33]	2	1.98
Diplopia [33]	2	1.98
Ocular movement disorder [33]	2	1.98
Decreased vision [3]	1	0.99

Table 3. The number of cases of initial clinical manifestation in KSS patients

Initial symptom (n=32)	Number of individuals	Percent (%)
Mental retardation [8]	2	6.25
Unknown [8]	7	21.9
Exercise intolerance [34]	1	3.12
Dizziness [3, 34]	4	12.5
Hearing loss [34]	2	6.25
Ptosis [3, 8, 34]	10	31.2
Visual symptoms [3, 8, 34]	3	9.38
Ataxia [8, 34]	2	6.25
Conscious disturbance [3]	1	3.12

Table 4. The number of cases of initial clinical manifestation in MERRF patients

Initial symptom (n=42)	Number of individuals	Percent (%)
Convulsions [3, 10, 36]	15	35.7
Headache [3]	2	4.76
Ataxia [3, 10, 36]	12	28.6
Myoclonic epilepsy [3, 10, 36]	7	16.7
Limb weakness [3, 36]	3	7.14
Conscious disturbance [36]	2	4.76
Fever [3]	1	2.38

shown in **Figure 7**. 18 patients had reduced muscle strength, eight patients had ataxia, 25 patients had pathology signs, 23 patients had abnormal tendon reflex, 46 patients had dystonia, 10 patients had nystagmus, 19 patients had ocular movement disorder, nine patients had mental disorder, seven patients had conscious disturbance and 19 patients had family history.

43 of 49 patients tested were found to have elevated lactic acid, four of 19 patients had abnormal cerebrospinal fluid and all of them had elevated protein content. 10 patients conducted ECG, 6 were found abnormal, including one heart block, and five arrhythmia. EEG was conducted in 25 patients; 17 of them were abnormal, showing spike wave, slow wave or both. Three of seven patients who performed EMG were abnormal, including one case of myogenic injury and two cases of neurogenic injury. 26 of CT-scanned 31 patients were found abnormal, 54 of 55 MRI-scanned patients were found abnormal, almost all showing symmetrical abnormalities (high density signals on T2 MRI and low density signals on CT) in the brainstem and basal ganglia. Seven patients conducted MRS; six had increased lactate and decreased N-acetyl aspartate. All 22 cases were positive on pathology examination and all 28 cases were DNA testing abnormal, including 16 COX deficiency, 3 mtDNA A8933G/C, one PDHA1 C214T, 3 mtDNA G13513A mutations and one mtDNA deletion.

LHON

LHON was the first described disease associated with hereditary point mutations in mtDNA [19]. Our study contained 160 LHON, the ratio of male and female was 124:36, and the ages ranged from 1.5 to 78 years, with a median age of 18 years. The highest proportion of initial symptom was visual loss (95.0%), followed by ataxia (3.75%), nystagmus (0.63%), atrophy of optic nerve (0.63%). Five patients had reduced muscle strength, 10 patients had pathology signs, 13 patients had abnormal tendon reflex, eight patients had dystonia, 67 patients had pallor papillae, 14 patients had abnormal color vision, 11 patients had atrophy of optic nerve, five patients had macroglossia, two patients had cavus and 92 patients had family history. All three patients tested were found to have elevated lactic acid, six out of 12 patients tested were found to have abnormal cerebrospinal fluid, all of them showed elevated protein content. Visual evoked potential (VEP) were conducted in 38 patients and all of them showed longer latency of P100. 44 patients received ECG, 16 were found abnormal with arrhythmia. EEG was conducted in two patients, both were abnormal. One of six patients who performed EMG was abnormal with a peripheral lesion. Three out of 25 CT-scanned patients were abnormal, 18 of 39 MRI-scanned

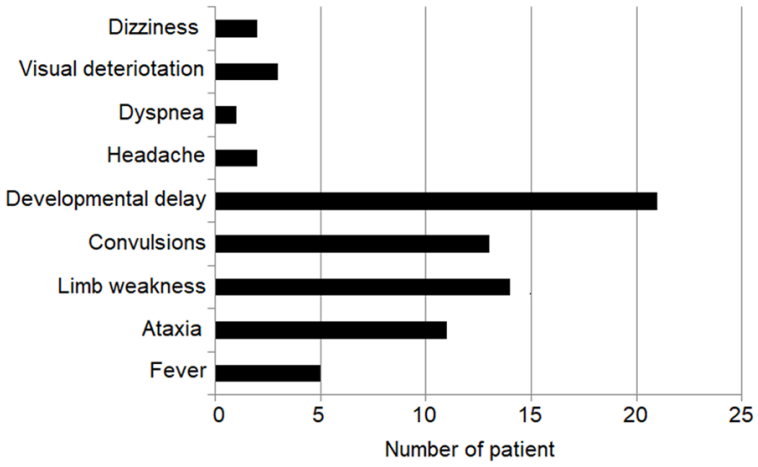

Figure 7. The number of cases of initial clinical manifestation in 72 LEIGH.

patients were found, most of them showed symmetrical abnormalities (high density signals on T2 MRI and low density signal on CT) in the lenticular nucleus and caudate nucleus. One patient conducted MRS, which showed increased lactate and decreased N-acetyl aspartate. Two patients had muscle biopsy, neither of the cases was positive. 129 cases conducted DNA testing, 55 had mtDNA G11778A, 10 had mtDNA G11779A, six had mtDNA T14484C, three had mtDNA G3460A, six had mtDNA G11696A, one had mtDNA G3635A and T14502C, one had mtDNA C11665T, T4216C and C4071T, and six had mtDNA T10197A mutations.

Others

MNGIE is an autosomal recessive disorder characterized by recurrent episodes of abdominal pain, nausea, vomiting, diarrhea, and pseudo-obstruction [8]. Three cases were included in the study as MNGIE, all were male. Two patients had onset of abdominal pain, vomiting and diarrhea, two patients had reduced muscle strength, none of the patients had pathology signs, or family history. Three patients tested were found to have elevated lactic acid, but cerebrospinal fluid was normal. Two patients who performed EMG were abnormal, showing neurogenic injury. None of the patients were found abnormal in CT or MRI examinations. All patients had muscle biopsy and were all positive. Three cases were abnormal in DNA testing, including two mtDNA A3243G and one mtDNA GT3271C mutations.

MELAS-Leigh is an overlap symptom of two diseases. Eight patients were included in this study as MELAS-Leigh. The ratio of male and female was 2:6, the ages ranged from 11 to 28 years with a median age of 19 years. The initial symptoms varied considerably, including two exercise intolerance, one mental retardation, two headache, one visual loss and one stoke. Three patients had reduced muscle strength, three patients had pathology signs, two patients had abnormal tendon reflex, four patients had dystonia, but none of patients had family history. Four of eight patients were found to have elevated lactic acid, but none of the patients were abnormal in cerebrospinal fluid. One patient conducted ECG and showed pre-excitation syndrome. EEG was conducted in two patients; both of them were abnormal, showing spike wave or slow wave. One patient who performed EMG was abnormal, with myogenic injury. Two patients received CT and were abnormal, seven of eight patients were found abnormal in MRI, almost all showing abnormalities (high density signals on T2 MRI and low density signals on CT) in the brainstem and basal ganglia. Four of eight cases were positive in pathological examinations. DNA testing was abnormal in all patients, including five mtDNA G13513A, one mtDNA GT-10191C, one mtDNA T13046C mutations and one mtDNA deletion.

Alpers disease is a progressive mitochondrial disorder characterized by myoclonic seizures and spasticity associated with liver involvement [8]. Our study contained five Alpers patients; the ratio of male and female was 3:2, the ages ranged from 10 to 32 years, with a median age of 20 years. The initial symptoms included three diarrhea, one convulsion and one visual loss. One patient had reduced muscle strength, none of the patients had pathology signs and four patients had family history. Two patients were found to have abnormal cerebrospinal fluid with increased protein content. One patient conducted ECG and was normal. EEG was conducted in three patients and was all abnormal, showing slow waves. One

patient who performed EMG was abnormal, with slow nerve conduct velocity. Two patients were abnormal in CT and two patients were found abnormal in MRI. Three out of eight cases were positive for pathology examinations. DNA testing was conducted in one patient and mtDNA was present.

A total of 30 cases were not classified because not enough information was available, however, 18 of them were confirmed by muscle biopsy, one was confirmed by DNA testing, and 11 were clinically confirmed.

Discussion

We summarized the clinical features in 912 mitochondrial encephalomyopathy patients in order to provide information for diagnosis and treatment. To our knowledge, this may be the first comprehensive investigation to examine the mitochondrial encephalomyopathies in China. The most common group was MELAS (50.3%) followed by LHON (17.5%), CPEO (11.1%), Leigh (7.89%), MERRF (4.61%), KSS (3.51%), MELAS-Leigh (0.88%), Alpers (0.55%) and MNGIE (0.33%). 3.29% were unclassified.

MELAS is a progressive multi-system disorder with onset typically in childhood; it was characterized by encephalopathy and subacute stroke-like events [20-22]. Other common clinical features of MELAS include migraine-like headaches, recurrent vomiting, weakness of extremities, and short stature with the highest initial symptom being headache (26.4%) [23]. In our cohort, headache was 46.3%, followed by convulsions (39.7%), stroke or seizures (24.2%), nausea or vomiting (16.4%), visual symptoms (14.7%), limb weakness (2.1%), conscious disturbance or mental disorder (8.79%), hearing loss (8.55%), ataxia (5.23%), and cognitive impairment (3.09%). Other common clinical features include short stature (38.8%), disturbance of intelligence (43.3%) and lactic acidosis (92.7%).

CT is widely available and is able to diagnose acute presentations of MELAS [24]. In our patients, 44.5% had low density signals in the cortex, 28% had basal ganglia calcifications, 18.7% had cerebral infarction, 17.6% showed cerebral atrophy, 2.75% showed high density signals in the cortical/basal ganglia/parenchyma junctions, and 0.55% showed white matter demyelination. MRI is widely used for MELAS diagnosis. Even if it cannot show pathognomonic features, the migration of the lesion and its inconsistency with the distribution of cerebral arteries would strongly suggest metabolic or mitochondrial disorders rather than arterial occlusion [25]. Based on MRI, the occipital lobe (69.8%) was the most diseased area, and the lesions were migrating and not consistent with the distributions of major arteries. MRS can assess metabolism in the brain metabolites, and has emerged as a useful tool for diagnosing MELAS [26, 27]. 84% of patients in this study were found to have increased lactate and decreased N-acetyl aspartate. Two patients showed reduced radioactivity in PET, this may be caused by decreased blood flow and glucose consumption and increased oxidative stress in the subacute phase [25].

Muscle biopsy is a confirmative assessment for MELAS, which can also role out other neuromuscular disorders. Ragged red fibers are the most typical manifestation of the muscle biopsy; some patients do not have RRF, but can have abundant accumulation of abnormal mitochondria under electron microscope. Moreover, increased SDH-positive fibers and amounts of COX-negative fibers can be seen. In our study, 93.9% of patients were positive for muscle biopsy, of which 336 cases showed RRF or abundant abnormal mitochondria, seven cases showed the demyelination or demyelination of the white matter in the cerebral hemispheres, degeneration of nerve cells and increased proliferation of glial cells and blood vessels. DNA testing is noninvasive and can identify mutations known to associate with MELAS. The testing can be performed on blood leukocytes, but because of mitotic segregation, some mitochondrial diseases can be identified only by using DNA isolated from muscle [8]. We found that 90.1% of patients tested had DNA abnormalities, of which 84.3% were mtDNA A3243G mutation, which is responsible for more than 80% of MELAS cases [28-30]. CPEO is a common manifestation of mitochondrial encephalomyopathies [31], which may be maternally inherited or autosomally inherited [32]. The course of CPEO is usually mild, patients may die because of aspiration pneumonia, circulatory-respiratory insufficiency or pulmonary embolism [33]. We found that the most

common initial symptoms are ptosis, accounting for 75.2% of the cases, 79.2% of patients have ocular movement disorder and 27.7% of patients have reduced muscle strength. None of them were neostigmine testing positive, which is a main differential point from myasthenia gravis. 65.4% of patients are positive in pathological examinations. CPEO is linked to either large deletions in mtDNA [34-36] or to various point mutations in tRNA molecules, including the np 3243 mutation which is more commonly associated with MELAS [37]. In our cohort, DNA testing was not performed for most cases, and was conducted only in 11 cases. Both mtDNA deletions and mtDNA mutation were detected. The deletions are 5000, 3533, 3059 and 3691 base-pair long and are different from 4977 base-pair deletion commonly known for CPEO [38].

KSS is characterized by chronic progressive extraocular muscle paralysis, pigmentary retinopathy and abnormal cardiac conduction [39, 40]. Patients often have a progressive limb myopathy and frequently require a pacemaker for atrioventricular block [14]. We found that in the KSS patients, the highest proportion of initial symptoms is ptosis, 90.9% of patients had elevated lactic acidosis and 76.7% of them had heart block. The commonest deletion, found in 30-50% of cases [41], is a 4.9 kb deletion. 96.4% of patients had RRF or abundant abnormal mitochondria under electron microscope.

MERRF is a maternally inherited disease characterized by myoclonic epilepsy, mental retardation, ataxia, muscle atrophy and sometimes hearing and vision loss [42-44]. Some patients develop symmetric lipomatosis in the neck and shoulders [8]. Renal insufficiency and cardiomyopathy occur in the patients [45]. The most common initial symptoms in this study are convulsions. 90.5% of patients had elevated lactic acid. 90.0% of patients had RRF or abundant abnormal mitochondria. Most patients with MERRF harbor a heteroplasmic mutation at np 8344 in the tRNALys gene [46]. Six out of 13 patients tested were found to have the mutation in addition to mtDNA A3243G mutation. The patients with mtDNA A8344G mutation showed limb weakness or ataxia, suggesting that the mutation may be related to cerebellar ataxia limb weakness.

Leigh's syndrome, also known as subacute necrotizing encephalopathy, is a neuropathological disorder with distinct clinical features mainly occurring during infancy [47]. The most common initial symptoms we observed are developmental delay. 87.8% of patients have elevated lactic acid. Brain imaging shows typically symmetrical abnormalities (high density signals on T2 MRI and low density signals on CT) in the brainstem and basal ganglia. The most frequent mtDNA mutations associated with Leigh syndrome are the T8993G and T8993C mutations in the ATPase6 gene, and the most frequently reported nDNA mutations associated with Leigh syndrome abnormality is COX deficiency [8]. In our study, 57.1% of patients has COX deficiency, 3-10% of patients have mutations at mtDNA 8993 and 13513 and 3.57% has PDH deficiency.

LHON is recognized as the commonest cause of isolated blindness in young men with an estimated incidence of 1 in 50,000 [48, 49]. We found that 95% of patients have decreased vision as their first symptom and they are abnormal in visual evoked potential (VEP). With the advance in molecular testing, a number of mtDNA mutations have been identified that help to diagnosis sporadic LHON cases [50, 51]. The mtDNA G11778A mutation is the most frequent mutation in LHON (in about 50-70% of patients), the G3460A mutation is present in 15-25% of the patients [52]. In our study, the percentages of the two mutation are less than reported [51-53], and different mutations such as mtDNA T14484C, G11696A, T10197A, G3635A and T14502C, 11665T, T4216C and C4071T were identified, suggesting there are considerable diversity of mtDNA mutations for the diseases.

MNGIE syndrome consists of leukoencephalopathy, external ophthalmoplegia, peripheral neuropathy, and intestinal dysmotility [54, 55]. All three patients in our study had abdominal pain, diarrhea and myasthenia. In addition, they all had elevated lactic acid and RRF. Multiple deletions in mtDNA are reported for MNGIE [26, 56, 57], however, only mtDNA mutations, but not deletion, were found in our cases. This may be attributed to small patient sample.

Alpers disease is often characterized by myoclonic seizures and spasticity associated with liver involvement. It is a rare disease and only five patients are included in our study. The first symptoms are diarrhea, myasthenia, vision

loss and seizure. RRF and mutation in the gene POLG1 are present in the patients.

MELAS-Leigh is not a common disease and is an overlap of MELAS and Leigh; therefore, it has the features of two diseases. Symptoms include exercise intolerance, mental retardation, epilepsy, headache, decreased vision, and stroke-like episode. Some patients could have WPW. MRI of all patients showed lesions in the bilateral basal ganglia and lobes or brainstem. The results of pathology were various, including RRF and trachychromatic SDH. mtDNA mutations and deletion are also found.

Treatment of mitochondrial disorders is supportive and aimed at stabilizing rather than reversing the disease [7, 58]. One of treatment strategies is early diagnosis and therapy for associated complications, such as seizures, diabetes mellitus, ptosis, cardiac conduction defects, and hearing loss. Another important aspect of treatment is administration of metabolites and cofactors, such as carnitine or coenzyme Q10. Gene therapy is being studied. Preventive therapy through genetic counseling and prenatal diagnosis is becoming increasingly important for nuclear DNA-related disorders [59] which may be applied to some of the diseases.

Our study still has several limitations. Most of the included studies were based on selective study samples, which may affect the distribution of various types of mitochondrial encephalomyopathies. Besides, the sample sizes of some mitochondrial encephalomyopathies are small, unable to present the whole situation. Nevertheless, the information presented in this study could provide assistance to diagnosis, management and treatment of the disease and useful insights for future research.

Conclusion

Nearly all types of reported mitochondrial encephalomyopathies are present in Chinese population. The age, onsets and clinical features are similar to what have been reported, but there are differences in mtDNA mutations. Noninvasive DNA testing may be applied for screening the disease as early as possible.

Disclosure of conflict of interest

None.

Abbreviations

mtDNA, mitochondrial DNA; nDNA, nuclear DNA; rRNA, ribosomal RNA; tRNA, transfer RNA; SDH, Succinate dehydrogenase; COX, Cytochrome C oxidase; NARP, Neurogenic muscle weakness with ataxia and retinitis pigmentosa; MELAS, Mitochondrial encephalomyopathy with lactic acidosis and stroke-like; MERRF, Myoclonic epilepsy and ragged red fibers; KSS, Kearns-Sayre syndrome; CPEO, Chronic progressive external ophthalmoplegia; MNGIE, Mitochondrial neurogastrointestinal encephalomyopathy; LHON, Leber's hereditary optic neuroretinopathy; RRF, Ragged-red fiber; PDH, Pyruvate dehydrogenase; MGT, Modified Gomori trichrome; NADH-TR, Nicotinamide adenine dinucleotide-tetrazolium reductase; PAS, Periodic acid-Schiff; MRS, Magnetic resonance spectroscopy; NAA, N-acetyl aminosuccinic acid; SPECT, single photon emission computed tomography; PET, Positron Emission Tomography; VEP, Visual evoked potential; TP, thymidine phosphorylase; NADH, nicotinamide adenine dinucleotide reduced; EMG, Electromyography; EEG, Electroencephalography; CT, Computed tomography; MRI, Resonance Imaging; DSA, Digital subtraction arteriography.

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