

Multisystem Disorder in Late-Onset Chronic Progressive External Ophthalmoplegia

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ABSTRACT: Introduction: Chronic progressive external ophthalmoplegia (CPEO) is a mitochondrial syndrome on a disease spectrum with Kearns-Sayre syndrome (KSS). Clinical presentation is variable and our experience suggested that phenotypic differences exist in CPEO with onset after age 20. **Methods:** This descriptive study is a retrospective chart review of 40 patients with late-onset CPEO. Clinical features, laboratory and neurophysiology results were reviewed. **Results:** Multisystem dysfunction was very common in this series. Gastrointestinal dysfunction was more common than expected (60%) as was migraine headache (40%). Clinical characteristics on the KSS disease spectrum were uncommon in this series with only 2.5% having pigmentary retinopathy, 5% with cardiac conduction abnormality, and 22.5% having endocrinopathy (most often thyroid dysfunction rather than diabetes). Neurophysiology abnormalities included length-dependent axonal polyneuropathy in 44% (sometimes subclinical) and myopathic EMG changes in 26%. Exposure to sources of acquired mitochondrial toxicity including cigarette use and hepatitis C infection were more common than expected in this series. **Discussion:** Phenotype was different in this late-onset series compared with previous reports in CPEO patients. In this series of late-onset patients, multi-organ dysfunction was more common than previously reported in CPEO, and some classical mitochondrial manifestations, such as pigmentary retinopathy were rare. We suggest that acquired mitochondrial toxicity may have a role in the pathogenesis of adult-onset CPEO.

RÉSUMÉ: Maladie multisystémique dans l'ophtalmoplégie externe progressive chronique à début tardif. Contexte : L'ophtalmoplégie externe progressive chronique (OEPC) est un syndrome mitochondrial qui se situe dans le spectre de maladies dont fait partie le syndrome de Kearns-Sayre (SKS). Sa présentation clinique est variable et, selon notre expérience, nous croyons qu'il existe des différences phénotypiques dans l'OEPC qui commence après l'âge de 20 ans. **Méthodes :** Il s'agit d'une étude descriptive de 40 patients atteints d'OEPC à début tardif dont nous avons révisé rétrospectivement les dossiers pour en tirer les observations cliniques, les données de laboratoire et les résultats d'études neurophysiologiques. **Résultats :** La dysfonction multisystémique était très fréquente chez ces patients. La dysfonction gastrointestinale (60%) et la migraine (40%) étaient plus fréquentes qu'attendu. Les caractéristiques cliniques du spectre du SKS étaient rares dans cette série de patients, seulement 2,5% étant porteurs d'une rétinopathie pigmentaire, 5% d'anomalies de conduction cardiaque et 22,5% d'endocrinopathies (la plupart du temps une dysfonction thyroïdienne plutôt qu'un diabète). Parmi les anomalies neurophysiologiques, nous avons retrouvé une polyneuropathie axonale longueur-dépendante chez 44% (parfois subclinique) et des changements de type myopathique à l'EMG chez 26%. Une exposition à des sources de toxicité mitochondriale acquise dont le tabagisme et l'infection par le virus de l'hépatite C était plus fréquente qu'attendu dans cette série de cas. **Discussion :** Le phénotype était différent chez nos cas à début tardif comparé à celui décrit dans les études publiées antérieurement. Chez nos patients atteints d'OEPC à début tardif, une dysfonction multisystémique était plus fréquente que chez les cas publiés antérieurement et certaines manifestations mitochondriales classiques telle une rétinopathie pigmentaire étaient rares. Nous proposons qu'une toxicité mitochondriale acquise puisse jouer un rôle dans la pathogenèse de l'OEPC débutant à l'âge adulte.

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Chronic progressive external ophthalmoplegia (CPEO) is a mitochondrial syndrome characterized by slowly progressive bilateral ptosis and ophthalmoparesis. Patients with CPEO have variable presentations ranging from pure CPEO to a CPEO "plus" syndrome with other accompanying multisystem features of mitochondrial disease. Classically these additional features include skeletal myopathy, pigmentary retinopathy (PR) and endocrine dysfunction.¹ These features place CPEO on a disease spectrum with Kearns-Sayre syndrome (KSS), another mitochondrial deletion syndrome characterized by CPEO, PR and onset earlier than 20 years-of-age, and frequently accompanied by other features of mitochondrial disease.²

Mitochondrial diseases are often difficult to diagnose because of their highly variable presentation and the absence of reliable non-invasive tests. These diagnostic challenges and variability in

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clinical presentation prompted this case series to further describe the clinical spectrum of the disorder in a population of patients with late-onset CPEO. Experience in our clinic suggested that the burden of multi-system manifestations of mitochondrial disease was high.

METHODS

This study is a retrospective chart review of patients referred to the Adult Metabolic Diseases Clinic in Vancouver, Canada from 2000 until 2008. Research ethics board approval was obtained. For inclusion patients were over 20 years-of-age with a diagnosis of CPEO made by two of the authors who are specialists in neuromuscular and metabolic diseases. For the purposes of this study, late-onset CPEO was arbitrarily defined as a patient with CPEO whose earliest symptoms of disease started after the age of 20. Diagnosis required characteristic clinical features (presence of slowly progressive ophthalmoparesis and ptosis in the absence of symptoms or signs of another aetiology) and was supported by muscle pathology and/or molecular genetic studies. Genetic testing included long-range polymerase chain reaction (PCR) with confirmation on Southern blot, and testing for other mitochondrial DNA point mutations (the panel includes A8344G (typically associated with MERRF), A3242G, T3721C and T3721deln (typically associated with MELAS)). Testing for nuclear DNA mutations associated with CPEO was requested in selected cases.

Findings on ocular examination were confirmed by a neuro-ophthalmologist. Laboratory testing to support the diagnosis of mitochondrial disease was obtained including pre- and post-prandial serum lactate, urine organic acid profile, and acylcarnitine profile. Alternative etiologies were excluded when appropriate with bloodwork (AChR antibody testing and oculopharyngeal muscular dystrophy DNA analysis), neurophysiology (electromyography (EMG), nerve conduction studies (NCS), single fiber EMG, and repetitive nerve stimulation) and neuroimaging (CT, and/or MR imaging of head and orbits, MR spectroscopy). Patients had screening for systemic complications of mitochondrial disease including endocrine and cardiac dysfunction, and when indicated by symptoms, screening of auditory and gastrointestinal systems.

Charts were identified for review from the clinic database, by searching for patients with a diagnosis of CPEO. Initially 45 subjects were identified, but five subjects were excluded because they did not meet entry criteria (two patients with fibre-type disproportion myopathy, and three patients with HIV and CPEO-

like syndromes on antiretrovirals, who were reported separately³). The remaining 40 charts were reviewed, to document demographic characteristics, age at diagnosis, age of onset of symptoms, and multisystem manifestations. The age of symptom onset was determined based on patients' and/or their families' self-report. The presence of ptosis, ophthalmoparesis, diplopia, PR and optic atrophy was recorded and confirmed by the neuro-ophthalmologist. Other possible neurological and systemic manifestations of mitochondrial disease were tabulated including: skeletal myopathy, exertional myalgias, fatigue, peripheral neuropathy, migraine headaches, seizures, stroke-like episodes, ataxia, sensorineural hearing loss, neuropsychiatric disorder, gastrointestinal disorder, cardiac or endocrine involvement. Ascertainment of more subjective complaints such as fatigue and neuropsychiatric symptoms of depressed mood and poor memory may not have been complete though when available psychiatric consultations or neuropsychology cognitive assessments were reviewed. Blood work indicated the presence of endocrinopathy (thyroid stimulating hormone [TSH], fasting glucose, serum and urine osmolality for diabetes insipidus), liver or renal involvement. Diagnostic tests confirmed polyneuropathy, skeletal myopathy (EMG/NCS), sensorineural hearing loss (audiometry) and cardiac disorder (ECG/echocardiogram/Holter monitor). Reports of neuro-imaging studies, including CT and MRI scans of the head, were reviewed. All of the above clinical features were questioned in every initial consultation. The prevalence of cigarette use, alcohol abuse, or chronic viral infection (HIV and hepatitis C virus [HCV]) were documented.

RESULTS

Refer to Table 1 for details regarding patient characteristics and Table 2 for multi-organ manifestations of mitochondrial disease. All of the subjects were from different families, except for one sibling pair. Diplopia was only intermittent and mild but found in 25/40 (62.5%) of patients. Skeletal muscle weakness preferentially affected the proximal musculature, and often coexisted with exertional myalgia. One patient had chest wall weakness and exertional dyspnoea. Gastrointestinal disorder present in 24 patients (60%) was most commonly dysphagia (18/24), followed by diarrhoea (5/24) and constipation (1/24). Subjective complaints of fatigue and neuropsychiatric disorders (including depression, bipolar illness and cognitive dysfunction) were common (42.5% and 37.5%, respectively), and coexisted in 9 (22.5%). Endocrine disorders (22.5%) were most frequently hypothyroidism (6/9), followed by diabetes mellitus (2/9) and one patient had multiple endocrine abnormalities, including diabetes insipidus, growth hormone deficiency and adrenal insufficiency. Pigmentary retinopathy was only found in one patient (2.5%). Cigarette use was documented in 20 (50%), alcohol abuse in two (5%) and chronic viral infections in four (10%, all HCV).

Laboratory investigations revealed that 11 (27.5%) patients had elevated serum lactate. Of the 39 patients who had EMG/NCS, 17 (44%) had an axonal sensory polyneuropathy which was subclinical in four patients, and was a sensorimotor neuropathy in three patients. Myopathic changes were present in ten patients (26%), and mild nonspecific EMG abnormalities were present in three. Sixteen patients (41%) had normal

Table 1: Age and sex of subjects with CPEO

Age (range)	54.5 (27-74)
Sex M:F	14:26
Average age at diagnosis	50.8
Average symptom duration pre-diagnosis (range)	11.8 (1-50)
Average number of multisystem manifestations (range)	4.6 (0-10)

EMG/NCS. Muscle biopsy was performed in 36 patients. Four patients did not have muscle biopsy because of an already confirmed diagnosis on genetic testing (two cases) or confirmed diagnosis in a direct relative (two cases). Characteristic findings of mitochondrial myopathy were present on histopathology in 26/36 patients (72%) and on electron microscopy (EM) in 17/26 (65%). Of the ten patients with nondiagnostic histopathology, four had findings on EM characteristic of mitochondrial disease. Genetic studies demonstrated the presence of single large-scale mtDNA deletions in 11/26 (42%) and nuclear mutations in three patients (all PolG1 mutations, including 1. Heterozygous T251I and P587L mutations; 2. heterozygous N1098I mutation; 3. Heterozygous A467T and G737R mutations (this patient reported previously in Milone et al⁴). Three of the patients with pathogenic genetic abnormalities had normal muscle histopathology (two with PolG1 mutations, and one with a 3.8 kb mtDNA deletion involving 70% of genomes). In total, the number of patients in this series with diagnosis proven by muscle pathology and/or genetic abnormalities was 35 (87.5%). Respiratory chain enzyme analysis performed on 12 of the biopsies provided diagnostic criteria in only one patient. Acylcarnitine and urine organic acid profiles were normal in all patients. Magnetic resonance imaging revealed non-specific white matter abnormalities in nine patients and thin extraocular muscles in three patients.

DISCUSSION

To our knowledge this series is the first of its kind to be directed specifically toward the study of clinical features of

CPEO patients with onset later than 20 years-of-age. This series reveals a number of differences in comparison with previously reported multisystem dysfunction in CPEO (Table 3). Pigmentary retinopathy was rare in our series, although the prevalence appears to be high in earlier-onset CPEO.^{1,5,6} Much lower rates have also been demonstrated although patients with earlier age of onset appeared more likely to have PR,⁷ and two other studies including patients from wide age ranges did not specify age for patients with PR.^{8,9} Our patient with PR had disease onset at age 20, with sensorineural hearing loss.

The frequent finding of intermittent diplopia suggests that the presence of diplopia should not exclude a slowly progressive disorder of ocular motility such as CPEO, as has been suggested previously.¹⁰ Endocrine disorder was less common than previously reported. The endocrine disturbance classically described with mitochondrial disease (and in particular KSS) is diabetes, although thyroid dysfunction is also well described.¹¹ In our series the majority of patients with endocrine disturbance had hypothyroidism. Gastrointestinal disorder occurred in 60%, and the large majority of these patients had dysphagia. Dysphagia was reported in 75% from a series of CPEO and KSS patients,¹² and in 30% of patients from another series of CPEO patients.⁷ Gastrointestinal manifestations are difficult to diagnose and probably under-recognized, but are potentially treatable.¹² The very frequent occurrence of migraine is another feature distinguishing this series from previously published series on CPEO and KSS. The high female to male ratio in this study has been reported in prior series with CPEO^{13,14} and is of undetermined importance, but may relate to variable penetrance or expressivity between sexes (as is seen in Leber hereditary optic neuropathy, another mitochondrial syndrome), or perhaps variable susceptibility to mitochondrial toxicity based on the effects of sex hormones.¹⁵ Some of the documented features such as fatigue and neuropsychiatric disorders were very common and would have benefited from more objective measurement.

Previous series of CPEO demonstrating high prevalence of KSS-like features have likely focused on earlier-onset patients, who may have more in common with KSS patients than late-onset CPEO patients. As examples of this, one series found that 33% of CPEO patients had elevated CSF protein,⁹ which is one of the diagnostic criteria for KSS. Furthermore, another study found that 11/22 CPEO patients with mtDNA deletions had PR, but only 1/10 patients without mtDNA deletions had PR,⁶ which is of interest given that KSS is a mtDNA deletion syndrome (and suggests that CPEO patients with PR are on a disease spectrum with KSS). In this series, late-onset CPEO patients appear to have a different constellation of multisystem dysfunction, with a more benign disease course and delayed onset of symptoms. We speculate this may be due to patients having subclinical mitochondrial genetic abnormalities (either from below-threshold heteroplasmy or variable penetrance) that are expressed phenotypically after acquired mitochondrial toxicity from ageing or environmental exposures.

Electron microscopy analysis demonstrated similar yield to histopathology, although four patients with diagnostic findings on EM had nondiagnostic histopathology. Ultrastructural analysis should therefore be pursued even in the presence of nondiagnostic histopathology as it may provide additional criteria for diagnosis in some cases. The occasional difference in diagnostic findings with histopathology and electron microscopy

Table 2: Prevalence of manifestations of CPEO and other features of mitochondrial disease

Symptom/sign	Number	Percentage
Ophthalmoplegia	40	100
Ptosis	40	100
Diplopia (intermittent)	25	62.5
Skeletal muscle weakness (on examination)	25	62.5
Gastrointestinal disorder	24	60
Sensorineural hearing loss	19	47.5
Fatigue	17	42.5
Migraine	16	40
Neuropsychiatric disorder	15	37.5
Exertional myalgia	14	35
Polyneuropathy (clinically and confirmed on NCS)	13	32.5
Endocrinopathy	9	22.5
• Hypothyroidism	6	15
• Diabetes mellitus (type II)	2	5
• Multiple	1	2.5
Ataxia	7	17.5
Cardiomyopathy	3	7.5
Cardiac conduction abnormality	2	5
Hemiparesis/stroke-like episodes	2	5
Optic atrophy	2	5
Pigmentary retinopathy	1	2.5

Table 3: Prevalence of multisystem manifestations of mitochondrial disease compared with prior study

	Present study (%)	Yamashita 2008⁹ (%)	Bau 2005¹ (%)	Sciacco 2001⁸ (%)	Laforet 1995⁷ (%)	Holt 1989⁶ (%)
GI disorder	60				30	
Polyneuropathy	44		23		21	
Migraine	40				21	
Pigmentary retinopathy	2.5	7	65	9	16	38
Endocrinopathy	22.5		67	N/A		
Hypothyroidism	15		N/A	N/A		
Diabetes mellitus	5		N/A	7*		
Cardiac conduction abnormality	5	10	26		19	
Skeletal myopathy	62.5	81		87	81	

is likely the effect of genetic mosaicism which appears to be quite complex in these conditions. Prior study has demonstrated genotype differences between and within individual muscle fibres within the same specimen.¹⁶ There may also be differences in sensitivity or specificity for electron microscopy in mitochondrial disease.

In this series mtDNA deletions were the most common genetic abnormality, which is consistent with prior reports.⁷ The relatively low yield of molecular genetic analysis in this series is likely explained by the limited panel of mtDNA and nuclear DNA mutations tested. Despite this limitation, three patients with positive genetic studies (two PolG1 mutations and one mtDNA deletion) had nondiagnostic muscle biopsy results. The finding of a nondiagnostic muscle biopsy with a large scale mtDNA deletion in CPEO has been reported once previously¹⁷ and emphasizes that genetic studies should always be included in the workup of mitochondrial disease.

The finding of thin extraocular muscles in some patients on CT and MRI may be under-reported in this series, given that only the radiology reports were reviewed. This abnormality has been studied previously in CPEO,^{18,19} and therefore may be useful in the workup of suspected cases, although the specificity of this finding remains unknown.

Ophthalmoplegia and ptosis have been described in association with antiretrovirals^{3,20} and statin medication.²¹ Presumably the cause is acquired mitochondrial toxicity relating to these agents. In a series of patients with HIV and antiretrovirals apparently causing CPEO, the phenotype appears to be quite similar to those in this series.³ Acquired mitochondrial toxicity may also play a role in the expressivity of Leber hereditary optic neuropathy.²² It is possible that other unidentified sources of acquired mitochondrial toxicity may be in part responsible for late-onset CPEO, potentially explaining phenotypic differences with early-onset CPEO, and this should be further investigated. In this series, sources of acquired mitochondrial toxicity such as cigarette smoking²³ and HCV infection²⁴ were more prevalent than expected (prevalence for British Columbia is 20.2% for smoking²⁵ and 0.8% for HCV²⁶). Remote alcohol abuse was documented in two patients. The

importance of these results is speculative and requires validation in larger series with quantification of the severity of exposures.

Limitations of this study include the fact that the age for symptom onset for adult-onset CPEO was arbitrarily chosen at 20 years. This age was chosen for the practical reason that adult neurologists are most likely to see this condition in patients with adult-onset of symptoms, as well as to exclude patients with KSS and improve the homogeneity of our study population. However, age of onset was based upon patients' self-report and therefore reporting of age of onset may not be fully reliable and it is possible some patients had onset earlier than age 20. Furthermore, it should be noted that not all patients had findings diagnostic for mitochondrial disease on muscle biopsy. We decided to include these patients in the review because in the practical sense, these patients do have a diagnosis of CPEO given their clinical syndrome and absence of alternative diagnoses after extensive investigation. It is well-known that definitive abnormalities on muscle biopsy are not present in all patients with mitochondrial disease, which may be related to heteroplasmy within tissues or the sampling of unaffected muscles.¹⁶ The alternative, which was to include only patients with diagnostic muscle biopsies, may have biased the findings away from the types of cases that would typically present to a clinical neurologist. Many patients did not have proven molecular abnormalities which was expected because of our limited panel available for point mtDNA mutations or nuclear DNA mutations.

CONCLUSIONS

In summary, this series presents the first review focusing exclusively on adult-onset CPEO patients. We have demonstrated phenotypic differences with prior series, and we suggest that acquired mitochondrial toxicity may interact with genetic abnormalities in the pathogenesis of adult-onset CPEO.

COMPETING INTERESTS

Dr. Sirrs has received speaking fees from Shire Human Genetics Therapies, and is an investigator in the Canadian Fabry Disease Initiative which receives partial funding from Shire Human Genetics Therapies and Genzyme Corporation.

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