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Disease impact in chronic progressive external ophthalmoplegia: More than meets the eye

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Abstract

We determined the extent of disease impact in 28 patients with genetically confirmed chronic progressive external ophthalmoplegia (CPEO) and compared the outcomes to those of matched myotonic dystrophy type I patients.

CPEO patients reported a high frequency of severe fatigue (67.9%), pain (96.2%), depression (32.1%) and dependency in daily life (46.4%). The frequency and extent of depression were significantly higher than in DM1 patients (32.1% vs. 7.1%, $p = 0.040$; mean Beck's depression inventory for primary care score 3.8 ± 3.5 vs. 1.3 ± 1.4 , $p = 0.001$), as were fatigue severity, pain intensity and extent of functional impairments.

CPEO patients with polymerase gamma-1 mutations reported more functional impairments than those with mitochondrial DNA mutations. Disease impact was however not influenced by most clinical features. The present results help physicians to identify and to treat the factors that influence quality of life in CPEO patients and to provide symptomatic treatment where needed.

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1. Introduction

Chronic progressive external ophthalmoplegia (CPEO) is one of the most common mitochondrial disorders in adults [1]. The defining symptom is a slowly progressive extraocular muscle weakness. Multi-system involvement is however common, causing functional impairments secondary to dysfunction of (proximal) skeletal muscles, retina, cochlea, cerebrum, cerebellum and heart [2].

The frequency and nature of these impairments (body level) are well documented in previous studies, but their impact on daily life activities (individual level) or participation (society level) are unknown [3–6]. In our experience, there is often a discrepancy between the generally mild

impairments and the severe limitations in activities and participation in CPEO patients. This discrepancy may lead to underestimation of disease impact by the treating physician, which in turn could result in inadequate symptomatic treatment at the level of activities and participation.

Here, we used a set of validated questionnaires to systematically determine disease impact on daily life activities and participation in a large cohort of CPEO patients from a single tertiary referral centre. In order to identify possible associations between disease impact and mutation type or clinical features we only included patients with a known causative mutation, and all participants underwent standardized neurological examinations. To estimate the clinical relevance of our results, we compared questionnaire outcomes of CPEO patients to those of matched myotonic dystrophy type I (DM1) patients. DM1 is suitable for comparison with CPEO since it is a relatively common

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neuromuscular disorder and therefore well known to many neurologists. Moreover, like CPEO, DM1 also affects muscle, eye, brain, and heart.

2. Methods

2.1. Patients

All CPEO patients known in Department of Neurology of the Radboud University Nijmegen Medical Centre were invited to participate. As there are no commonly accepted criteria for CPEO, we only included patients with both characteristic clinical features and a known causative mutation [2]. Consequently, all participants met the following three criteria:

- (1) a phenotype including a slowly progressive bilateral external ophthalmoplegia,
- (2) a proven pathogenic mutation or deletion in the mitochondrial DNA (mtDNA) or in the nuclear polymerase gamma 1 (POLG1), Twinkle or adenine nucleotide translocator 1 (ANT1) genes,
- (3) exclusion of an alternative diagnosis.

These inclusion criteria also cover two more or less specific mitochondrial phenotypes with external ophthalmoplegia as a key symptom: the Kearns–Sayre syndrome (KSS: ophthalmoplegia, pigmented retinopathy, age of onset below 20 years, and at least one of the following symptoms: cardiac conduction block, cerebellar ataxia, elevated CSF protein content) and SANDO (Sensoric Atactic Neuropathy, Dysarthria and Ophthalmoplegia) [7–9]. In the present study, we used the term CPEO to describe all patients meeting the inclusion criteria and the terms KSS and SANDO to describe the specific subtypes only.

Age and sex matched controls were selected from a previously published cohort of genetically confirmed, adult onset DM1 patients, all of whom attended normal education [10]. All participants gave informed consent. Local ethical committee approved this study and the patients' consent was obtained according to the Declaration of Helsinki.

2.2. Questionnaires

We used a set of validated questionnaires to evaluate several important determinants of disease impact:

2.2.1. Fatigue severity

Experienced fatigue is defined as an overwhelming sense of tiredness, lack of energy and feeling of exhaustion. We used the Checklist Individual Strength (CIS) to determine the severity of experienced fatigue [11]. CIS is a 20-item questionnaire, which measures the severity of fatigue in four different sub items: fatigue severity (8 items, range 8–56), reduced concentration (5 items, 5–35), reduced activity (3 items, range 3–21), and reduced motivation (4

items, range 4–28). Each item was scored on a seven-point scale. A CIS fatigue score equal to or higher than 35 indicates severe fatigue [11,12].

2.2.2. Pain

Analgesic use and intensity and location of pain were assessed with the McGill's Pain Questionnaire (MPQ) [13]. Pain intensity was scored on a 100 mm horizontal visual analogue scale (VAS) and was divided in minimal, actual and maximal VAS scores. Patients could allocate pain to one or more of 32 predefined body areas.

2.2.3. Depression

Depression was rated according to the Beck's Depression Inventory for Primary Care (BDI-PC) [14]. This is a 7 item self-report instrument composed of cognitive and affective symptoms. Each item is scored on a 4-point scale. Scores equal to or higher than 5 indicate depression [14]. BDI-PC was preferred over the complete BDI to avoid an overlap between physical aspects of fatigue and the somatic symptoms of depression.

2.2.4. Functional impairments and independency

Functional impairments were assessed with the Dutch version of the Sickness Impact Profile (SIP-136) [15]. The 136 items are divided into 12 categories: sleep and rest, emotional behavior, body care and movement, household management, mobility, social interaction, ambulation, alertness and intellectual functioning, communication, work, recreation and pastimes, and eating. The SIP-136 has no validated cut off value, as healthy controls are by definition free of disease related functional impairments.

The level of independency was assessed with the modified Rankin scale (mRS), a 7-point observer rated scale. The mRS scores 0–2 indicate independency in daily life activities [16]. In all questionnaires, higher scores indicate more disability.

2.3. Statistical analysis

Data analysis was performed using SPSS (version 17.0) for Windows. An independent Mann–Whitney *U*-test was used to compare means and a Fisher's exact test to compare frequencies. Correlations were calculated using a Spearman coefficient and odds ratios using a binary logistic regression. Significance level was set at $p < 0.05$ (two-tailed) in all cases.

3. Results

3.1. Patients

We identified 30 patients meeting the inclusion criteria. All were invited to participate, two male patients (one with an m.12315G>A mutation and one with a mtDNA deletion) refused because of a lack of motivation. In general, their clinical features and disease severity were in the same

Table 1
Demographic, genetic and clinical data of 28 CPEO patients.

No.	Sex/age/age at onset	Mutation	Cerebellar ataxia	Periph. neurop.	Dysarthria	Cognitive impairm.	Proximal myopathy	Retinal/cochlear involv.	Other
1	F/41/32	Deletion	–	–	–	–	–	–/+	HT
2	F/28/17	Deletion	–	–	–	–	+	–/–	
3	F/33/14	Deletion	–	–	–	–	–	–/–	M
4	M/30/8	Deletion	+	–	–	+	+	+/+	
5	F/49/25	Deletion	–	–	–	–	+	–/–	
6	F/57/34	Deletion	–	–	–	–	+	–/–	CM, E
7	M/51/25	Deletion	–	–	+	–	+	–/–	
8	M/43/14	Deletion	+	–	+	+	+	+/+	CB
9	F/50/13	Deletion	–	–	–	–	+	–/–	
10	F/56/17	Deletion	–	–	–	–	–	–/–	
11	M/57/12	Deletion	–	–	+	–	+	–/–	
12	F/45/5	Deletion	–	–	–	–	–	–/–	
13	F/35/25	Deletion	–	–	–	–	–	–/–	
14	F/42/26	Deletion	–	–	–	–	+	–/–	
15	F/37/12	Deletion	+	–	+	–	+	+/+	
16	F/54/29	Deletion	+	–	+	+	+	+/+	AF
17	M/55/30	m.5709T>C	–	–	–	–	–	–/–	O, E, C
18	M/54/48	m.4267A>G	–	–	–	–	+	–/–	
19	F/50/12	m.3243A>G	+	–	+	–	+	–/+	DM, M
20	M/49/12	m.3243A>G	–	+	–	+	–	–/+	DM
21	M/75/54	POLG1	–	+	+	–	+	–/–	
22	F/42/30	POLG1	+	SAN	+	–	+	–/–	
23	M/54/35	POLG1	+	SAN	+	+	+	–/–	
24	F/48/25	POLG1	+	SAN	+	+	+	–/–	
25	M/46/39	POLG1	+	SAN	+	+	+	–/–	
26	M/39/23	POLG1	+	SAN	+	–	+	–/–	
27	F/48/24	POLG1	+	SAN	+	–	+	–/+	
28	M/46/21	POLG1	+	SAN	+	+	–	–/–	

Abbreviations: age and age at onset in years; C, cataract; CB, cardiac conduction block; CM, cardiomyopathy; DM, diabetes mellitus; E, epilepsy; HT, hypothyroidism; M, migraine; O, otosclerosis; POLG1, polymerase gamma 1; SAN, sensoric atactic neuropathy.
+ presence of symptom; – absence of symptom.

range as the participants. Of 28 participants (12 men, 16 women), 16 patients had a single mtDNA deletion, 4 a pathogenic mtDNA point mutation and 8 a POLG1 mutation (Table 1). POLG1 mutations included a homozygous A467T in six patients and compound heterozygous A467T and W748S mutations in two (patients 27 and 28). None of the patients had Twinkle or ANT1 mutations. Mean disease duration was 23.3 ± 10.6 years and mean age of onset was 23.6 ± 11.7 years. Three patients met the criteria for KSS and 7 for SANDO.

3.2. Questionnaires

3.2.1. Fatigue severity

Severe fatigue (CIS fatigue score ≥ 35) was the most frequent complaint, being reported by 19 patients (67.9%) with a mean CIS fatigue score for the whole group of 40.0 ± 12.6 . Demographic characteristics, clinical features, mutation type, and outcomes on all other questionnaires did not differ between patients with or without severe fatigue.

3.2.2. Pain

CPEO patients mainly reported pain in the upper legs and head (Fig. 1). Only one patient (3.6%) reported no pain (actual, minimal and maximal VAS scores = 0 mm). Twelve patients (42.9%) reported pain on waking up, of whom 5 had moderate to severe pain. Ten patients (28.6%) reported limitations in daily activities due to pain. Among the 27 patients with pain, sixteen (59.3%) used analgesics, mostly acetaminophen (13 patients, 48.1%), NSAIDs (7 patients, 25.9%) and opioids (2 patients, 7.4%). Patients using analgesics had higher CIS reduced concentration (21.1 ± 10.0 vs. 13.5 ± 8.3 , $p = 0.036$) and SIP sleep and rest scores (104.8 ± 64.1 vs. 47.6 ± 33.2 , $p = 0.033$) than patients without analgesic use, while there were no differences in pain severity.

3.2.3. Depression

Depression (BDI-PC score ≥ 5) was found in 9 patients (32.1%) and mean BDI-PC score was 3.8 ± 3.5 . Only 2 of the nine patients with a depression used antidepressants, together with 2 non-depressed patients. Depression was

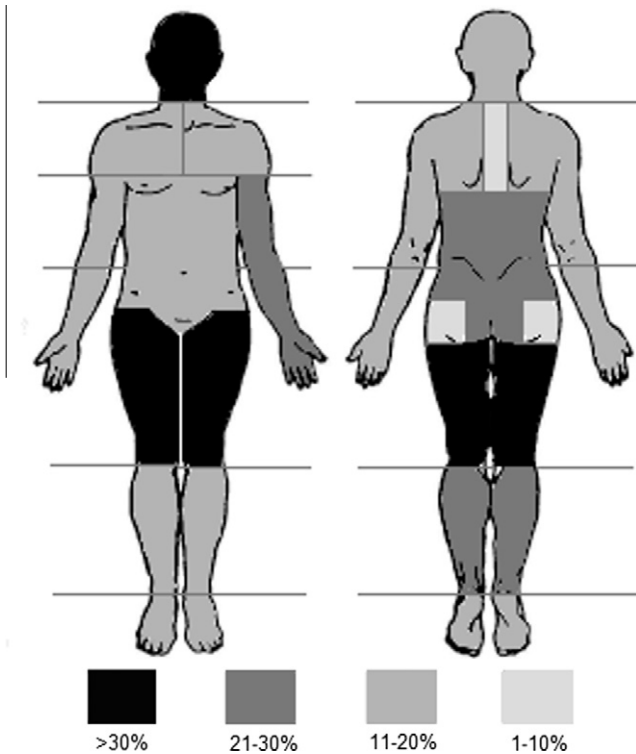


Fig. 1. Distribution of pain in CPEO patients showing the percentage of patients with pain in 32 predefined body areas.

associated with various other determinants of disease impact: depressed patients had higher CIS reduced motivation (20.3 ± 4.6 vs. 14.5 ± 6.4 , $p = 0.012$), CIS reduced activity (16.7 ± 3.6 vs. 11.4 ± 6.1 , $p = 0.030$) and total CIS scores (101.2 ± 16.9 vs. 80.7 ± 26.1 , $p = 0.049$) compared to non-depressed patients. Moreover, depressed patients were less likely to be independent ($mRS \leq 2$) in daily life activities (11% vs. 74%, $p = 0.004$) and had more severe functional impairments (total SIP score 2993 ± 1380 vs. 1621 ± 1320 , $p = 0.017$). This difference in total SIP score mainly consisted of significantly higher subscores on emotional behavior (204.9 ± 149.8 vs. 74.0 ± 120.7 , $p = 0.010$), body care and movement (580.1 ± 428.7 vs. 267.2 ± 348.6 , $p = 0.025$), mobility (248.7 ± 158.4 vs. 81.6 ± 189.6 , $p = 0.005$), social interaction (463.6 ± 274.4 vs. 209.7 ± 243.1 , $p = 0.018$), and ambulation (257.6 ± 110.9 vs. 124.9 ± 116.8 , $p = 0.005$).

3.2.4. Functional impairments and independence

Fifteen patients (53.6%) were independent in daily life activities ($mRS \leq 2$), whereas 13 (46.4%) were not ($mRS > 2$). Patients who were independent in daily life activities had lower CIS reduced motivation (13.8 ± 5.3 vs. 19.2 ± 6.6 , $p = 0.015$), CIS reduced activity (10.5 ± 5.5 vs. 16.4 ± 5.1 , $p = 0.011$), and total CIS scores (75.4 ± 25.6 vs. 101.1 ± 16.8 , $p = 0.009$) compared to patients who were not independent. As expected, non-independent patients reported more severe functional impairments (total SIP score 2659 ± 1175 vs. 1584 ± 1616 , $p = 0.018$), with significantly higher SIP subscores on body care and movement (497.8 ± 392.9 vs. 255.1 ± 377.3 , $p = 0.017$), mobility

Table 2
Aspects of disease impact in patients with CPEO and DM1.

	CPEO (n = 28)	DM1 (n = 28)	
<i>CIS</i>			
Fatigue	40.0 ± 12.6	34.0 ± 10.5	$p = 0.035$
Concentration	17.9 ± 10.0	18.1 ± 6.2	
Motivation	16.4 ± 6.4	14.1 ± 6.2	
Activity	13.1 ± 5.9	9.8 ± 5.4	$p = 0.044$
<i>BDI-PC</i>	3.8 ± 3.5	1.3 ± 1.4	$p = 0.001$
<i>MPQ</i>			
Actual VAS pain	22.5 ± 24.6	9.1 ± 12.1	$p = 0.028$
Minimal VAS pain	12.0 ± 14.9	7.7 ± 15.4	$p = 0.045$
Maximal VAS pain	63.3 ± 27.2	30.6 ± 33.8	$p = 0.001$
<i>SIP</i>			
Sleep and rest	93.9 ± 78.6	68.2 ± 61.0	
Emotional behavior	116.1 ± 142.3	15.3 ± 29.9	$p = 0.001$
Body care and movement	367.8 ± 397.0	201.0 ± 184.4	
Household management	228.2 ± 180.4	124.0 ± 86.6	$p = 0.026$
Mobility	135.3 ± 194.2	48.8 ± 91.9	
Social interaction	291.3 ± 276.2	109.7 ± 155.4	$p = 0.002$
Ambulation	167.5 ± 129.3	146.8 ± 125.5	
Alertness	224.4 ± 216.9	137.5 ± 132.0	
Communication	161.8 ± 168.3	103.9 ± 121.7	
Work	160.0 ± 159.4	130.3 ± 144.9	
Recreation and pastimes	114.7 ± 95.7	85.9 ± 76.3	
Eating	22.8 ± 45.1	4.8 ± 19.2	$p = 0.022$
Total	2083 ± 1505	1176 ± 821	$p = 0.031$

Abbreviations: DM1, myotonic dystrophy type 1; CIS, Checklist Individual Strength; BDI-PC, Beck's Depression Inventory for Primary Care; MPQ, McGill's Pain Questionnaire; VAS, Visual Analogue Scale; SIP, Sickness Impact Profile.

Scores are expressed as mean \pm SD.

(191.0 ± 164.2 vs. 87.1 ± 210.3 , $p = 0.043$), social interaction (377.7 ± 235.9 vs. 216.5 ± 294 , $p = 0.021$), and ambulation (237.6 ± 119.4 vs. 106.8 ± 107.3 , $p = 0.004$), and communication (239.2 ± 191.2 vs. 94.7 ± 113.5 , $p = 0.032$).

3.3. CPEO vs. DM1 patients

To estimate the clinical relevance of our findings, we compared questionnaire results of CPEO patients to those of age and sex matched DM1 patients. CPEO patients were more often depressed than DM1 patients (32.1% vs. 7.1%, $p = 0.040$). In addition, CPEO patients had higher CIS fatigue, CIS reduced activity and VAS scores and more severe functional impairments, indicated by a higher total SIP score (Table 2). The higher total SIP score mainly consisted of significantly higher subscores on emotional behavior, household management, social interaction and eating. Except for CIS reduced concentration, scores on all other questionnaires were non-significantly higher in CPEO than in DM1 patients.

3.4. Influence of clinical features or mutation type on disease impact

Several clinical features were associated with an increased risk of depression (Table 3). In contrast, none of the clinical features was associated with severe fatigue

Table 3

Odds ratios indicating the relation between clinical features and three aspects of quality of life: fatigue, depression and functional impairments.

	Severe fatigue (CIS fatigue ≥35)	Depression (BDI-PC ≥5)	Non-independent (mRS >2)
Cerebellar ataxia	0.5 (0.1–2.3)	9.8 (1.5–63.8)*	4.4 (0.9–21.8)
Peripheral neuropathy	1.2 (0.2–6.2)	7.5 (1.3–44.1)*	4.7 (0.9–24.8)
Dysarthria	0.7 (0.1–3.5)	2.8 (0.5–14.4)	4.5 (0.9–22.1)
SANDO phenotype	0.5 (0.1–3.1)	10.6 (1.5–76.1)*	4.1 (0.6–26.1)
Cognitive impairment	0.7 (0.1–4.0)	6.7 (1.1–40.4)*	2.5 (0.5–13.5)
Proximal myopathy	1.4 (0.3–7.8)	4.7 (0.5–45.5)	3.7 (0.6–22.8)
Retinal involvement	1.5 (0.1–16.8)	2.4 (0.3–20.8)	4.2 (0.4–46.5)
Cochlear involvement	1.6 (0.3–10.2)	3.0 (0.5–16.7)	2.5 (0.5–13.5)

Abbreviations: CIS, Checklist Individual Strength; BDI-PC, Beck's Depression Inventory for Primary Care (BDI-PC); mRS, modified Rankin scale; SANDO, sensoric atactic neuropathy, dysarthria, ophthalmoplegia. Expressed as odds ratio (95% confidence interval).

* $p < 0.05$.

or non-independency in daily activities, though there was a strong tendency towards an association between non-independency and cerebellar ataxia, peripheral neuropathy and dysarthria. Also, fatigue severity, depression, pain and level of independency were not influenced by sex, age or disease duration.

The SANDO phenotype was only present in patients with POLG1 mutations, while only one of the patients with POLG1 mutations had a clinical phenotype different from SANDO.

Patients with POLG1 mutations had more functional impairments (i.e. a higher total SIP score), with higher SIP subscores on body care and movement, household management, social interaction, ambulation, and communication (Table 4). The percentage of patients being independent in daily activities did not differ between patients with POLG1 mutations and patients with mitochondrial DNA mutations or deletions (mRS 0–2: 75% vs. 35%, $p = 0.096$). However, moderately severe disability (mRS = 4: unable to walk without assistance and unable to attend to own bodily needs without assistance) was more common in patients with POLG1 mutations (50.0% vs. 11.1%, $p = 0.032$). Fatigue severity, depression and pain did not differ between patients with or without POLG1 mutations. However, depression was more common in patients with SANDO phenotype than in patients with non-SANDO phenotypes (71% vs. 19%, $p = 0.020$).

4. Discussion

We showed that severe fatigue, depression, pain and functional impairments contribute to disease impact in CPEO patients. We also found that disease impact was related to the mutation type, as patients with POLG1 mutations had more severe functional impairments than patients with mtDNA mutations or deletions.

Table 4

Aspects of disease impact in CPEO patients with mtDNA mutations or deletions (non-POLG1) versus patients with POLG mutation (POLG1).

	CPEO Non-POLG1 (n = 20)	CPEO POLG1 (n = 8)	
<i>Demographics</i>			
Sex (M:F)	7:13	5:3	
Age	45.8 ± 9.3	49.8 ± 11.1	
Age at onset	20.5 ± 10.7	31.4 ± 11.1	$p = 0.041$
Disease duration	25.3 ± 11.4	18.4 ± 6.3	
<i>CIS</i>			
Fatigue	40.7 ± 12.9	38.5 ± 12.4	
Concentration	18.1 ± 10.7	17.3 ± 8.3	
Motivation	15.1 ± 5.4	19.5 ± 7.9	
Activity	12.6 ± 6.0	14.4 ± 5.9	
<i>BDI-PC</i>	3.6 ± 3.7	4.5 ± 2.9	
<i>MPQ</i>			
Actual VAS pain	25.3 ± 23.5	15.0 ± 27.5	
Minimal VAS pain	12.8 ± 13.9	9.7 ± 18.6	
Maximal VAS pain	65.6 ± 23.8	57.1 ± 36.3	
<i>SIP</i>			
Sleep and rest	100.1 ± 82.1	78.6 ± 71.9	
Emotional behavior	120.1 ± 150.2	106.1 ± 129.1	
Body care and movement	204.3 ± 208.8	776.4 ± 471.7	$p = 0.001$
Household management	172.6 ± 138.6	367.1 ± 206.1	$p = 0.019$
Mobility	103.7 ± 195.4	214.4 ± 178.4	
Social interaction	206.6 ± 248.1	503.3 ± 235.0	$p = 0.003$
Ambulation	122.4 ± 98.9	280.5 ± 132.4	$p = 0.007$
Alertness	213.4 ± 229.1	251.9 ± 194.6	
Communication	113.0 ± 127.1	283.8 ± 203.8	$p = 0.032$
Work	158.9 ± 158.3	162.8 ± 173.3	
Recreation and pastimes	103.8 ± 100.2	142.0 ± 82.8	
Eating	16.6 ± 40.2	38.5 ± 55.4	
Total	1635 ± 1317	3205 ± 1421	$p = 0.011$
Modified Rankin scale	2.2 ± 1.0	3.3 ± 0.9	$p = 0.017$

Abbreviations: CIS, Checklist Individual Strength; BDI-PC, Beck's Depression Inventory for Primary Care; MPQ, McGill's Pain Questionnaire; mtDNA, mitochondrial DNA; POLG1, polymerase gamma 1; VAS, Visual Analogue Scale; SIP, Sickness Impact Profile.

Scores are expressed as mean ± SD.

We demonstrated that severe fatigue, defined as an overwhelming sense of tiredness, lack of energy and feeling of exhaustion was present in the majority of CPEO patients. Moreover, we found that severe fatigue was more common in CPEO than in DM1 or in several other neuromuscular disorders [17]. The excessive fatigue reported by CPEO patients could in part be attributed to exercise intolerance, a key symptom in mitochondrial myopathies [18]. However, the CIS fatigue questionnaire which we used to rate fatigue severity covers multiple aspects of fatigue. CIS fatigue questionnaire scores were uniformly high on all aspects and we therefore think that fatigue in CPEO is more than exercise intolerance alone.

The high frequency of depression in this study is consistent with previous reports on CPEO as well as reports on other mitochondrial disorders [19–25]. It is however, in contrast to other chronic neuromuscular disorders such as DM1, hereditary motor and sensor neuropathy type I and facioscapulohumoral dystrophy, which are not

associated with an increased risk of depression [17]. This discrepancy between mitochondrial disorders and other neuromuscular disorders suggests a causative relation between mitochondrial dysfunction and an increased risk of depression. This concept is supported by the previously reported association between mood disorders and decreased cerebral metabolic activity [26–28]. The frontal lobes may play a particularly important role in the development of depression in mitochondrial disorders since they have an important function in mood regulation, carry a relatively high percentage of mutant mitochondrial DNA and have a relatively high metabolic demand [29–31].

Patients with POLG1 mutations had more functional impairments than patients with mtDNA point mutations or deletions, despite a (non-significantly) shorter disease duration. Since there were no differences in concentration, motivation, activity and depression, these aspects of disease impact cannot explain the increased functional impairments in patients with POLG1 mutations. POLG1 mutations were however strongly associated with a sensoric atactic neuropathy, which is a debilitating syndrome and may therefore account for the increased functional impairments in patients with POLG1 mutations [32].

To estimate the clinical relevance of our results, we compared questionnaire outcomes of CPEO patients to those of matched DM1 patients. Although disease impact in DM1 is commonly considered to be profound, CPEO patients more frequently and more seriously suffered from depression, pain and functional impairments in several domains (emotional behavior, household management, social interaction, and eating), while fatigue severity and limitations in almost all other domains were at least equal to DM1 [33,34].

Literature on disease impact in CPEO is limited. The present results confirm and extend previous findings of limitations in health related physical and common role activities, and perception of impaired general health and vitality in CPEO patients [35]. However, in contrast to our results, this previous study found normal subjective perception of mental health and normal social activities, and a low frequency of depression. The discrepancy between the former and the present study might be explained by the fact that we used a more extensive set of validated questionnaires to evaluate a wider range of quality of life aspects.

This study has several methodological limitations. First, the cross sectional design makes it impossible to determine the direction of associations. A longitudinal study design should be performed to differentiate between causes and consequences. Second, although our study population is one of the largest ever published in a prospective clinical study on genetically confirmed CPEO patients, sample size is still small for extensive statistical analysis. As a consequence, possible relations and correlations might not be detected. Since CPEO is a rare disorder, inclusion of more genetically confirmed patients is very difficult. Last, this is a single centre study from a tertiary referral clinic. Our study population might therefore not be representative for the total population of CPEO patients. However, since the

prevalence of CPEO is low and the diagnosis of CPEO requires specialized techniques, nearly all CPEO patients in the Netherlands are referred to a tertiary referral clinic. Moreover, since this study has a high participation rate, we think that the study population is indeed representative.

In conclusion, CPEO causes a profound impact on social and daily life activities, which is indeed more than meets the eye. From our data we conclude that management of CPEO patients should include screening for the main aspects of disease impact: fatigue, depression, pain, and functional impairments. As there is no cure for CPEO, symptomatic treatment of these aspects may improve quality of life. For this purpose we suggest a multidimensional approach aimed at the specific needs of the individual patient. This approach may include rehabilitation and medication for the treatment of depression or pain.

Author contributions and disclosures

B.S., G.B. and B.vE. conceived the original protocol and initiated and executed the study. J.F., C.D. and J.K. collected the data. B.S. analyzed the data and drafted the manuscript. B.S. and B.vE. drafted the final manuscript.

None of the authors has any conflicts of interests regarding this study.

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