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The Wide Phenotypic Spectrum of Adult-Onset Single Large-Scale Mitochondrial DNA Deletion Syndromes

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ABSTRACT

Single large-scale mitochondrial DNA deletions (SLSMDs) give rise to a wide spectrum of clinical features, including Kearns–Sayre syndrome (KSS) and chronic progressive external ophthalmoplegia (CPEO). Because longitudinal data are scarce, the natural history remains poorly defined. This study was undertaken to describe the clinical spectrum in a large cohort of patients with clinical onset after 16 years of age. A retrospective multicenter study was performed in patients diagnosed and followed in seven European mitochondrial disease centers. Seventy patients were included. The median age at disease onset was 27 years, and the median age at last evaluation was 52 years, with a median follow-up duration of 19 years. Median survival from disease onset was 34 years. KSS spectrum disorder was present in 36% of the patients, while CPEO was identified in the remaining 64%. Among those with CPEO at onset, 27% progressed to KSS spectrum disorder. Multisystem involvement was present in 59%. The most frequently reported symptoms or signs were ptosis and/or ophthalmoplegia (100%), skeletal muscle weakness (56%), perceived fatigue (34%), visual impairment (30%), exercise intolerance (33%), pigmentary retinopathy (20%), hearing impairment (19%), cardiac conduction block (15%), ataxia (11%), epilepsy (14%), and cognitive impairment (11%). Our study gives further insight into the highly heterogenous clinical presentation and natural history associated with SLSMDs. The relevance of categorizing patients into classical syndromic phenotypes may be questioned, as the observed overlap in clinical manifestations and the frequent evolution of phenotype over time suggest a continuum of disease expression rather than clearly distinct syndromic entities.

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1 | Introduction

Primary mitochondrial disorders, affecting 12.5 in 100 000 of the adult population [1], are an important cause of neurological disease, often with additional multiorgan involvement. Together, they constitute a rising number of over 340 monogenic disorders caused by defects in either the nuclear or the mitochondrial genome [2]. Single large-scale mitochondrial DNA deletions (SLSMDs) were the first identified genetic cause of mitochondrial disease [3]. The deletion typically occurs de novo, although a recurrence risk of 4% in the offspring of affected mothers has been reported [4]. It is one of the most common causes of primary mtDNA disorders in adults, contributing to 13% of mitochondrial disease cases with an estimated prevalence between 1.2 and 1.6/100 000 [5, 6].

Most patients with SLSMDs have progressive multisystem involvement, which is typically classified into one of three overlapping SLSMD syndromes (SLSMDSs): Pearson syndrome (PS), Kearns–Sayre syndrome (KSS), or chronic progressive external ophthalmoplegia (CPEO) [7].

KSS was first described in 1958, and its classical diagnostic criteria were proposed in 1982. These criteria consist of the triad of onset before age 20 years, pigmentary retinopathy, and external ophthalmoplegia together with at least one of the following features: heart block, cerebrospinal fluid (CSF) protein concentration greater than 100 mg/dL, or cerebellar ataxia [8, 9]. PS was originally defined by the combination of sideroblastic anemia and exocrine pancreatic dysfunction [10]. It has not been described with an adult onset, but those who survive PS in childhood commonly also develop KSS later in life [11]. CPEO is typically less severe and characterized by progressive ptosis, external ophthalmoplegia, oropharyngeal weakness, proximal limb weakness of variable severity, and the absence of multisystem involvement. Patients with CPEO who exhibit multisystem involvement but do not meet the diagnostic criteria for KSS have often been classified as having "CPEO-plus". However, many individuals with SLSMDs display phenotypes that do not strictly conform to the traditional definitions of KSS, CPEO, or PS [12–20]. In particular, the age-at-onset threshold for KSS has been regarded as arbitrary, whereas CPEO-plus lacks a universally accepted definition. These limitations underscore the phenotypic overlap among disorders associated with SLSMDs [20–22]. To better capture this variability, broader classification criteria were proposed in 2015 under the term "KSS spectrum," encompassing the continuum of overlapping phenotypes [15]. In addition, SLSMDs may present as less severe mitochondrial myopathies or with atypical features, including Leigh syndrome or MELAS [17, 23, 24].

A diagnosis of SLSMDS is suspected based on characteristic clinical symptoms and signs, findings on biochemical screening, muscle morphology changes, or decreased activity of OXPHOS complexes in a tissue sample. The diagnosis is confirmed by molecular genetic testing.

There is no approved disease-modifying treatment for SLSMDSs. Treatment is mainly directed at symptomatic manifestations of the multisystemic disease. Dietary supplements are frequently given but are of uncertain efficacy [25, 26]. There are emerging treatments in preclinical or early clinical phases [27–30]. Assessing treatment efficacy in a clinical trial for SLSMDSs is difficult because of the complex and heterogeneous phenotype, including fluctuating clinical course, multiple organ system involvement, and limited availability of natural history data and established outcome measures [25]. Better understanding of the natural history is important to facilitate early diagnosis and follow-up programs adapted to the patients' needs.

There are a few larger cohort studies of the natural history of patients with SLSMD and adult disease-onset [12, 13, 18, 20, 31, 32], with most clinical reports published so far describing small numbers of patients and not the development of symptoms and signs over time. In this retrospective study, we aimed to describe the phenotypic spectrum and disease outcome in a large European multicenter cohort of 70 individuals with SLSMD and disease-onset at or after 16 years of age.

2 | Methods

2.1 | Study Design and Population

The study was conducted as a retrospective analysis in seven European centers specializing in mitochondrial diseases: Gothenburg, Copenhagen, Rotterdam, Stockholm, Oulu, Helsinki, and Bergen. The Regional Ethical Review Board of Gothenburg approved the whole study and waived informed consent. Each participating center received local ethical approval and complied with the requirements of their local regulatory authorities.

The inclusion criterion was the presence of a pathogenic single large-scale mtDNA deletion exceeding 1.1 kb, as previously defined [33]. Patients with multiple mtDNA deletions were not included.

Data were collected with the help of an electronic case report form (CRF) into a centrally administered database, similarly to the network's earlier study on Leigh syndrome and POLG-related diseases [34, 35]. CRF design, clinical definitions, and criteria were decided collectively in the study design phase by mitochondrial network experts from all centers. Collected data included family history; medical history and survival status; clinical, biochemical, histological, and neuroimaging findings; and received treatment. Participating experts at each study center collected and reviewed data. Sample monitoring of data entry consistency was conducted by the first author.

For this analysis we, selected from the database those with a disease onset at 16 years of age or later (Figure 1). Disease onset was defined as the earliest occurrence of disease-related findings, including the first observation of a major clinical feature (e.g., the debut of a chronic manifestation of ptosis, external ophthalmoplegia, muscle weakness, visual impairment, exercise intolerance, fatigue, cardiac conduction block, hearing impairment, muscular atrophy, or pigmentary retinopathy) by the patient, family members, or healthcare professionals, as documented in medical records. Not all data were available for all patients;

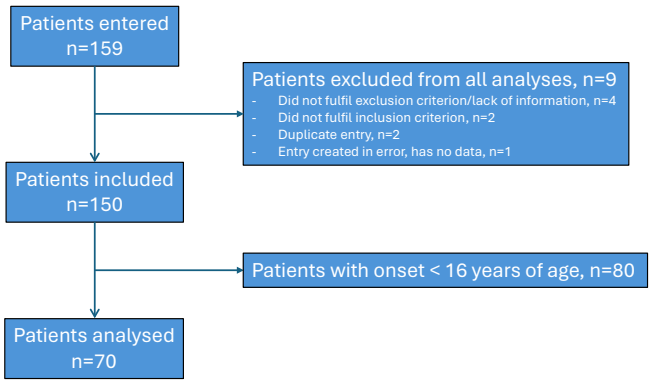

FIGURE 1 | Patient disposition.

where data are lacking, it has been noted in tables and text and excluded from calculations.

We followed the 2015 classification criteria [15] to address the issues with the classical phenotype definitions and distinguish the groups of "KSS spectrum" (defined as SLSMD with ptosis and/or ophthalmoparesis and at least one of the following: retinopathy, ataxia, cardiac conduction defects, hearing loss, failure to thrive/short stature, cognitive involvement, tremor, and cardiomyopathy), PS (SLSMD with refractory anemia), and CPEO (SLSMD with ptosis and/or ophthalmoparesis without fulfilling KSS spectrum or PS criteria). Phenotypic grouping was based on patients' phenotype at the last follow-up. Patients who progressed from CPEO to the KSS spectrum were classified within the KSS spectrum group.

2.2 | Clinical Definitions

Hearing impairment was defined as ≥20 dB hearing loss at <18 years of age, or ≥26 dB hearing loss at ≥18 years of age. Short stature was defined as height less than 2 SD below the mean for age and sex using center standards. Dementia was defined as decline of memory and thought processes for a period of at least 6 months, as confirmed by cognitive testing. Intellectual disability was defined by IQ below 70.

2.3 | Statistical Analysis

Statistical analysis was performed using SAS analysis software version 9.4 and MedCalc version 19.8. Due to the rarity of the disease, the study was not powered for specific statistical hypotheses, and the statistical evaluations were considered exploratory.

3 | Results

3.1 | Demographics and Family History

A total of 70 individuals matched the inclusion criteria, 44 females and 26 males, none of whom were genetically related. Of these, 94% were of European descent. There was no known parental consanguinity, and no known mitochondrial disease in relatives. The mean time from disease onset to last follow-up was 21.3 (range 0.0–50.8) years. The mean age at the last evaluation was 51.1 years (range 20.7–83.1).

3.2 | Genetic Findings

All patients underwent genetic testing that confirmed the presence of an SLSMD in either muscle or blood. The methods used for genetic analyses varied among sites over time and included southern blot analysis ($n = 32$), long-range polymerase chain reaction ($n = 19$), multiplex ligation-dependent probe amplification ($n = 2$), restriction fragment length polymorphism ($n = 1$), quantitative polymerase chain reaction ($n = 1$). For 30 patients, the genetic analysis method could not be discerned.

The median time between disease onset and the first investigation was 11.3 (range 0.0–49.0) years. Due to differences in methodological approach among centers and over time, the exact deletion breakpoints were known for 31 (44%) patients, while only the approximate deletion length was known for the remaining 39 (56%) patients. The 4977-base pair common deletion was confirmed in six patients.

Heteroplasmy level of the deletion in muscle was known for 39 patients (Supplemental Table 1). All skeletal muscle samples showed heteroplasmy (mean 43%), while the deletion was occasionally undetectable in analyses of blood, cavum oris epithelium, and urine sediment, where heteroplasmy levels were markedly lower than in skeletal muscle. Heteroplasmy in the levator palpebrae superioris muscle of two patients was 25% and 56%, while the respective heteroplasmy in skeletal muscle was 20% and 16%.

3.3 | Muscle Pathological and Biochemical Findings

Muscle biopsy was performed in 43 patients. Muscle pathological changes indicative of mitochondrial disease were seen in all 17 patients within the KSS spectrum group and in 25 of 26 patients in the CPEO group. Histopathological findings included ragged-red fibers in 34 patients (79%), cytochrome c oxidase deficiency in 32 (74%), abnormal mitochondrial proliferation in 7 (16%), and lipid accumulation in 5 (12%).

Respiratory chain enzyme activities in muscle tissue mitochondria were analyzed in 33 patients. Abnormal enzyme activities were observed in 5 of 14 patients within the KSS spectrum group and in 10 of 19 in the CPEO group. Isolated Complex I deficiency was identified in two patients, isolated Complex IV deficiency in two patients, isolated Complex V deficiency in one patient, while combined deficiencies were observed in 10 patients.

CSF lactate levels were within the normal range in the five patients with available data, whereas lactate levels in blood were elevated in 17 of 38 patients. No significant difference in lactate levels, either in blood or CSF, was observed between the KSS spectrum and CPEO groups.

CSF protein levels were available for eight patients and were elevated in three patients within the KSS spectrum group and in two patients in the CPEO group.

3.4 | Major Clinical Phenotypes

Adhering to the 2015 classification criteria, 25 patients (36%) were classified within the KSS spectrum, defined by the presence of ptosis and/or ophthalmoplegia accompanied by additional clinical features. The remaining 45 patients (64%) were classified as CPEO, characterized by ptosis and/or ophthalmoplegia in the absence of additional KSS spectrum features. No patients fulfilled the criteria for PS. For comparison, patients were also classified based on the classical 1982 criteria. Two patients (3%) fulfilled the diagnostic criteria for classical KSS, while 29 patients (41%) met criteria for CPEO without multisystem involvement. The remaining 39 patients (56%) met criteria for CPEO and additionally exhibited multisystem involvement.

Multisystem clinical features other than myopathy were observed during the disease course in 41 patients (59%). Among patients within the KSS spectrum group (Supplemental Table 2), the extent of multisystem involvement varied, with involvement of three or four organ systems being most common. Although patients in the CPEO group did not meet the additional KSS spectrum criteria as defined by the 2015 classification, 16 patients (36%) exhibited additional multisystem clinical features (Table 1; Supplemental Table 3).

3.5 | Disease Course

The median age at disease onset was 27.3 years (range 16.8–74.0) (Figure 2). The age at disease onset was highly similar between the KSS spectrum group (mean 30.0 years, median 29.4, range 18.0–72.9) and the CPEO group (mean 29.7 years, median 25.0, range 16.8–74.0). Onset before 20 years of age was observed in 4 patients (16%) in the KSS spectrum group and in 10 patients (22%) in the CPEO group. Nine patients fulfilled KSS spectrum criteria at disease onset. Among the 44 patients who initially presented with CPEO and for whom longitudinal data were available, 12 (27%) subsequently progressed to the KSS spectrum over a period ranging from 1.3 to 55.5 years (median duration of 21.8 years).

The age of onset of major clinical features is shown in a box-and-whisker plot in Figure 3. Ptosis, retinopathy, and PEO tended to present early during the disease course, whereas hearing impairment appeared later.

Acute exacerbations requiring hospitalization were reported in two of 49 patients with available data, one of whom required intensive care. The patient admitted to intensive care presented with respiratory failure accompanied by diffuse neurologic, ophthalmological, endocrine, and gastrointestinal involvement, while the other hospitalized patient experienced perceived fatigue and ophthalmological symptoms. No underlying causes for acute exacerbations were identified.

Clinical manifestations observed throughout the disease course are summarized in Table 1.

3.6 | Survival

Based on the last recorded status for each patient, 62 patients were alive, 7 had died, and one was lost to follow-up. The cause of death was available for only one patient, who died of astrocytoma. The median age at death was 58.7 years (range 42.9–68.0), and the median time from disease onset to death was 34.0 years (range 19.5–48.3). There was no significant difference in survival probability from disease onset between CPEO and KSS spectrum groups (log rank test $p = 0.41$; Figure 4).

3.7 | Neuroimaging and Spectroscopy

Brain magnetic resonance imaging (MRI) was performed in 20 patients at a median age of 45.5 years (range 20.2–73.7). MRI findings were normal in 14 of 20 patients (70%). Abnormalities were more common among patients with KSS spectrum disorder, with five of nine patients (56%) demonstrating generalized cerebral atrophy and white matter changes. In contrast, only 1 of 11 patients (9%) with CPEO showed MRI abnormalities, consisting of increased supratentorial T2 signal without evidence of atrophy.

Follow-up MRI was available in three patients after 1.3–8.3 years and showed no significant radiological progression. Magnetic resonance spectroscopy was performed in one patient with KSS spectrum and showed no abnormalities.

4 | Discussion

In this large European multicenter cohort study of patients with SLSMDSs and adult disease onset, we describe a median diagnostic delay of 11 years, indicating diagnostic difficulties and possibly not enough recognition of this group of disorders in healthcare. Genetic diagnosis is not always straightforward, as tissue-specific heteroplasmy may lead to failure to detect the deletion in blood cells. As a result, a skeletal muscle biopsy is often required to establish a molecular diagnosis [36]. Nevertheless, a recent study reported improved detection of SLSMDs in peripheral blood, likely reflecting advances in molecular diagnostic methodologies [18]. A diagnostic clue from the muscle biopsy is the presence of histopathological evidence of a mitochondrial myopathy, which was found in all but one of our patients who underwent a biopsy. In contrast, the biochemical investigations of the muscle mitochondrial function were normal in about 50%. Similar to the findings in our study of SLSMDSs with childhood-onset [37], none of the patients reported a family history of mitochondrial disease. This contrasts with an earlier study of 226 families with SLSMDs, which identified recurrence in 3 of 73 offspring of affected probands [4].

Our findings are difficult to compare directly with previous studies because of differences in study design. Earlier cohort studies have either been limited by small sample sizes [18, 20], focused on a broader range of mitochondrial disorders or genotypes [38–41], examined a specific clinical phenotype [3, 19, 32, 42–45], or investigated predictors of disease progression [13, 14, 31]. Other studies have provided more limited descriptions of the clinical characteristics associated with disease onset in adulthood [15, 17, 22, 46].

TABLE 1 | Clinical manifestations during the disease course.

	CPEO	KSS spectrum	Total
Central nervous system and sensory organs			
Progressive external ophthalmoplegia	100% (45/45)	100% (25/25)	100% (70/70)
Perceived fatigue	28% (11/39)	44% (11/25)	34% (22/64)
Visual impairment	14% (5/36)	54% (13/24)	30% (18/60)
Pigmentary retinopathy	n/a	55% (11/20)	20% (11/55)
Hearing impairment	n/a	52% (12/23)	19% (12/64)
Epilepsy[a]	10% (4/42)	21% (5/24)	14% (9/66)
Neuropsychiatric symptoms	5% (2/41)	20% (5/24)	12% (8/65)
Cerebellar ataxia	n/a	29% (7/24)	11% (7/63)
Dementia and/or intellectual disability	n/a	32% (7/24)	11% (7/65)
Migraine	5% (2/40)	12% (3/25)	8% (5/65)
Optic atrophy	0% (0/31)	18% (3/17)	6% (3/48)
Use of hearing aid	n/a	13% (2/15)	4% (2/47)
Neuromuscular			
Skeletal muscle weakness	48% (20/42)	71% (17/24)	56% (37/66)
Weakness in limb muscles	43% (18/42)	67% (16/24)	52% (34/66)
Exercise intolerance	32% (9/28)	33% (7/21)	33% (16/49)
Muscular atrophy	14% (5/37)	30% (6/20)	19% (11/57)
Peripheral neuropathy	2% (1/41)	14% (3/22)	6% (4/63)
Cardiac			
Conduction block[b]	n/a	40% (10/25)	15% (10/65)
Hypertrophic cardiomyopathy	n/a	17% (4/24)	6% (4/64)
Pacemaker treatment	n/a	16% (4/25)	6% (4/65)
Dilated cardiomyopathy	n/a	8% (2/24)	3% (2/64)
Endocrine			
Short stature[c]	n/a	68% (17/25)	26% (17/66)
Diabetes mellitus	7% (3/42)[d]	13% (3/24)[e]	9% (6/66)
Hypothyroidism	2% (1/42)	13% (3/24)	6% (4/66)
Adrenal insufficiency	0% (0/42)	4% (1/24)	2% (1/66)
Growth hormone deficiency	0% (0/42)	0% (0/23)	0% (0/65)
Other			
Hepatic disorder	3% (1/39)	8% (2/24)	5% (3/63)
Chronic diarrhea	0% (0/38)	12% (3/25)	5% (3/63)
Hematological disorder[f]	0% (0/39)	12% (3/25)	5% (3/64)
Renal disorder	0% (0/39)	8% (2/25)	3% (2/64)
Exocrine pancreatic dysfunction	0% (0/42)	0% (0/23)	0% (0/65)

Note: Numbers in parantheses indicate number of patients with the finding/number of patients for which data were available. Age at onset for Type 2 patients ranged from 35.8 to 59.6 years.
Abbreviation: n/a, not applicable because of classification criteria.
[a]Only two were receiving antiepileptic treatment at the time of last follow-up.
[b]Two with first degree atrioventricular block (AVB), one with second degree AVB, three with third degree AVB, one with right bundle branch block (RBBB) with left anterior hemiblock, one with RBBB with left anterior fascicular block and two with isolated RBBB.
[c]8/24 (33%) males and 9/42 (21%) females.
[d]Type 1, $n = 2$; Type 2, $n = 1$.
[e]Type 1, $n = 1$; Type 2, $n = 2$.
[f]One with pernicious anemia, one with ongoing anemia due to renal failure, and one with ongoing general anemia with unknown cause.

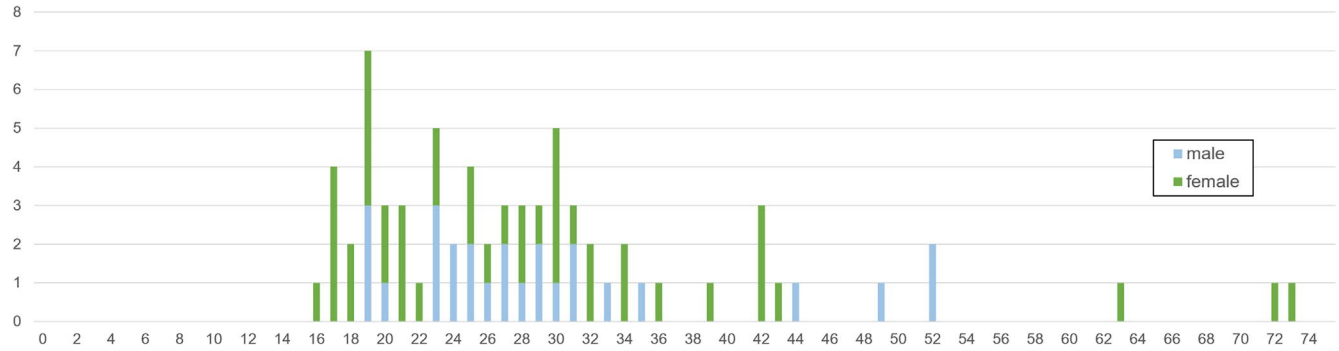

FIGURE 2 | Age at disease onset. *Note:* Distribution of age at disease onset in years, by gender (26 male and 44 female patients).

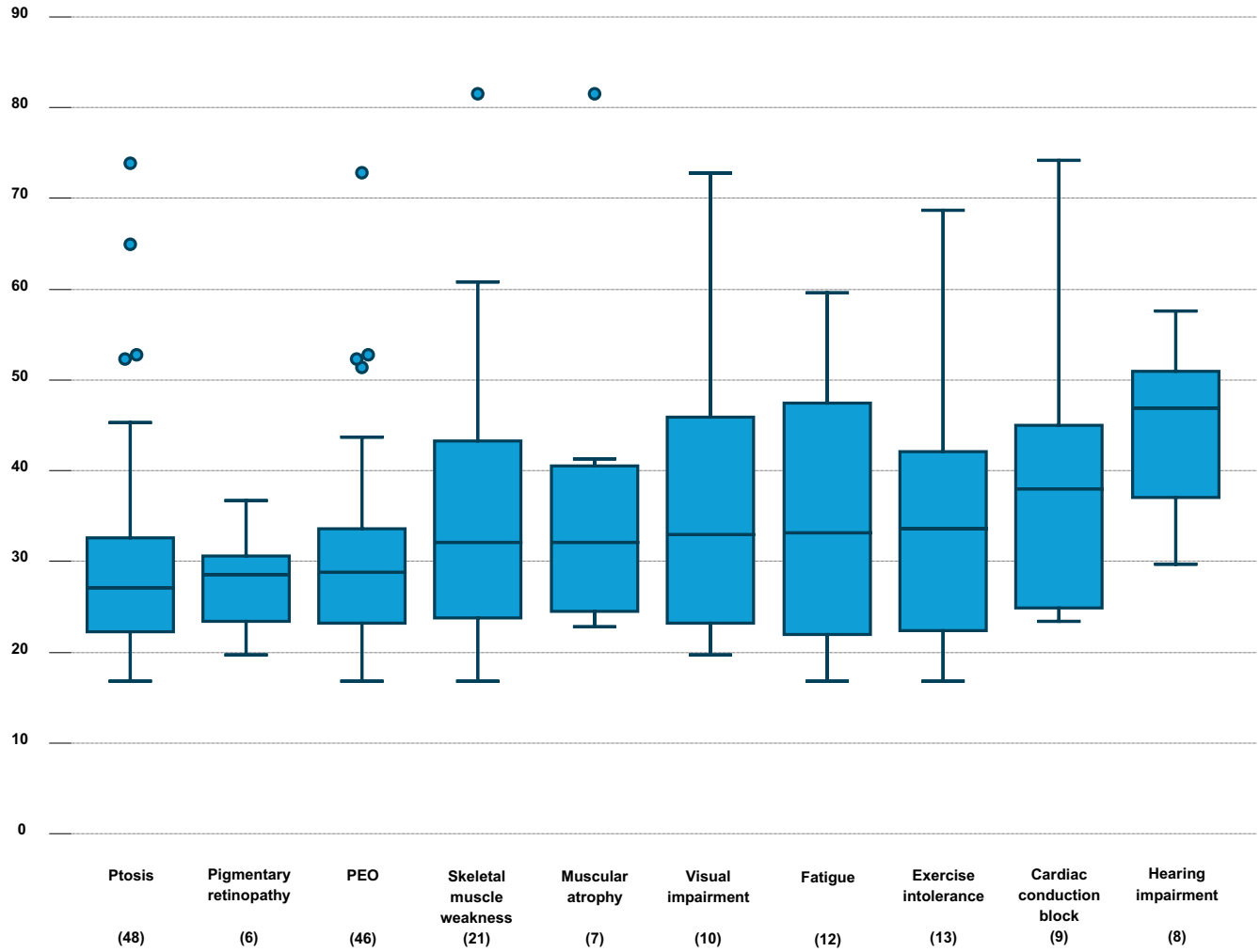

FIGURE 3 | Onset age of major clinical features. Number in parentheses indicates the number of patients for which the onset age was known. PEO, progressive external ophthalmoplegia.

The distinction between KSS spectrum and CPEO may be less clear-cut than traditionally assumed. In our cohort, 27% of the cases initially classified as having CPEO progressed to a KSS spectrum phenotype during follow-up, supporting the notion of a phenotypic continuum. Moreover, the similar median age at diagnosis and the median survival from disease onset observed in the two groups suggest that KSS spectrum disorder and CPEO may represent different stages or degrees of severity within the same disease process rather than entirely distinct phenotypes. A recent report of 30 SLSMDS patients also found evolving phenotypical presentation and increasing symptoms with age [18]. The disease progression appears to be multidimensional rather than following a common trajectory, suggesting that classification into discrete groups may be less informative for predicting disease course in adult-onset patients. Alternative prognostic strategies have therefore been explored, including the use of disease burden scales combined with genetic data and multiple regression analysis [13]. Others have sought to improve prognostic stratification by refining the distinction between KSS and CPEO through adjustment of the age-at-onset cutoff [22].

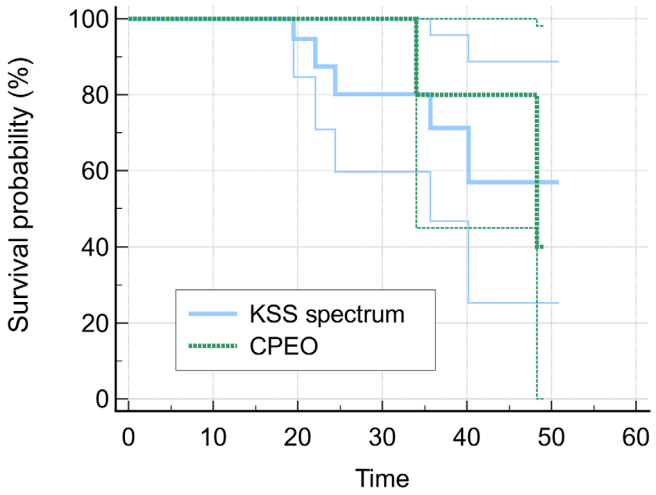

FIGURE 4 | Survival of patients since disease onset. *Note:* Kaplan–Meier analysis of survival since disease onset for patients with CPEO phenotype versus patients with KSS spectrum phenotype. Thin lines indicate 95% confidence interval.

Progressive external ophthalmoplegia was found in all and ptosis in 99% of the patients in this study; thus, these findings should raise a strong suspicion of a mitochondrial disease. The prevalence increases with age and is a hallmark of SLSMDSs [31, 37]. While pigmentary retinopathy, visual impairment, and hearing impairment were less common than in our childhood-onset group, they were still reported in 18%–30% of the adult-onset patients.

Muscle weakness was the most frequent extraocular symptom and was as common as that seen in our patients with childhood onset. In contrast, exercise intolerance was more frequently reported, identified in 33% of the patients. It was recently reported as the most common extraocular symptom in a Chinese cohort of patients with SLSMDs, detected in 40% of CPEO patients [22]. Exercise intolerance, frequently associated with dyspnea and tachycardia and sometimes without obvious symptoms or signs at rest, is an important diagnostic clue that, when present in a patient, should raise a strong suspicion about an underlying metabolic myopathy [47].

Even though CNS involvement was less common compared to what is seen in our patients with childhood onset, it was still present in nearly half of the adult-onset patients. While dementia and psychiatric manifestations have been described in many different mitochondrial diseases [48, 49], the impact of dementia/cognitive decline or psychiatric disease in SLSMDSs has seldom been described in previous studies. A cross-sectional neuropsychological study of 15 adult SLSMD patients did not reveal signs that would suggest general intellectual decline but rather focal deficits of visuospatial and executive functions [50]. Perceived fatigue, reported in over one-third of our cohort, has been identified as an important factor for disease burden that often severely impacts functionality in mitochondrial diseases [51]. While cerebellar ataxia is part of the classical criteria for KSS, it was only present in 29% of KSS spectrum patients in this study. In comparison to many other mitochondrial diseases, both epilepsy and peripheral neuropathy were minor features. Acute exacerbations were rare compared to what was seen in our childhood-onset group [37].

Progression to other organ system involvement was less common in our adult-onset cohort when compared to the childhood-onset cohort [37], albeit not rare, since almost one in 10 developed cardiac conduction block or cardiomyopathy after disease onset. The importance of regular cardiac evaluation is further emphasized by an international multicenter study, which identified a risk of a major adverse cardiac event from either heart failure or arrhythmia in > 20% of the patients over a 10-year follow-up from baseline [52]. In our study, short stature was a common finding, and diabetes mellitus and hypothyroidism were occasionally reported. Liver or renal involvement was rare, and none of the patients developed sideroblastic anemia or pancreatic insufficiency. The findings of our study underscore the importance of regular follow-up in these patients to facilitate the early identification and monitoring of evolving disease manifestations.

This study has several limitations. Its retrospective design and non-epidemiological nature may introduce bias. Age at first symptom onset relied on patient or family recall and may therefore be imprecise, particularly given the gradual disease progression. Some clinical signs and symptoms overlap with manifestations commonly associated with normal aging, making it difficult to determine whether they are attributable to the underlying mitochondrial disease. This may have led to an overestimation of their prevalence in our cohort. Conversely, such findings may also have been underreported if they were considered age-related and therefore not documented in the medical records. Although the multicenter design enabled inclusion of a relatively large cohort, differences in historical clinical practices between centers may have introduced confounding despite predefined study protocols. Genetic testing methods varied across centers, and in many cases the specific methods used could not be verified. This reflects the long diagnostic history of many patients and may have affected diagnostic accuracy or caused imprecise or biased estimation of heteroplasmy levels. Furthermore, some historical testing methods have been shown to occasionally misinterpret other molecular rearrangements as SLSMDs [53, 54]. The issue of possible overestimation bias of heteroplasmy calculation with PCR-based methods has led to the development of new PCR-free sequencing approaches [55]. Reassessment of genetic results with contemporary genetic methods was not feasible within this study.

A key strength is the relatively long follow-up period. In contrast to the predominantly small case series available to date, this cohort of 70 patients with adult-onset disease provides a more comprehensive characterization of the clinical features and outcomes, thereby adding to existing knowledge.

Adult-onset SLSMDS is a multisystemic disease with diverse organ manifestations, which necessitates a structured multidisciplinary multiorgan follow-up. Given the retrospective design, less typical manifestations were likely underreported. Prospective natural history studies are needed to better characterize disease progression and to optimize care for these patients.

Author Contributions

Kristoffer Björkman: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, software, validation, visualization, writing original draft preparation, writing – review and editing. **Niklas Darin:** conceptualization, funding acquisition, investigation, methodology, supervision, resources, validation, writing original draft preparation, writing – review and editing. **Mar Tulinius:** conceptualization, funding acquisition, investigation, methodology, supervision, resources, validation, writing – review and editing. **Elsebet Østergaard:** investigation, methodology, resources, writing – review and editing. **Irenaeus de Coo:** investigation, methodology, resources, writing – review and editing. **Martin Engvall:** investigation, methodology, resources, writing – review and editing. **Gittan Kollberg:** investigation, methodology, resources, writing – review and editing. **Karin Naess:** investigation, methodology, resources, writing – review and editing. **John Vissing:** investigation, resources, writing – review and editing. **Kari Majamaa:** investigation, resources, writing – review and editing. **Omar Hikmat:** investigation, resources, writing – review and editing. **Christopher Lindberg:** investigation, resources, writing – review and editing. **Kristin N. Varhaug:** investigation, resources, writing – review and editing. **Pirjo Isohanni:** methodology, resources, writing – review and editing. **Johanna Uusimaa:** methodology, resources, writing – review and editing.

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Ethics Statement

Ethical approval for the whole study was received from the Regional Ethical Review Board of Gothenburg (Dnr 557-13, 289-17, 106-04) and from the local ethical committees by each participating center as per local regulatory requirements.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available upon reasonable request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Supplemental Table 1.** Heteroplasmy levels. **Supplemental Table 2.** Overview of system involvement in the KSS spectrum group. **Supplemental Table 3.** Overview of system involvement in the CPEO group.