Oculopharyngodistal myopathy is a distinct entity - clinical and genetic features of 47 patients

Hacer Durmus, MD1, Steven H. Laval, DPhil2, Feza Deymeer, MD1, Yesim Parman, MD1, Esen Kiyam, MD3, Munever Gokyigit, MD4, Cumhur Ertekin, MD5, Ibrahim Ercan, MD4, Seyhun Solakoglu, MD6, Veronika Karcagi, PhD7, Volker Straub, MD2, Kate Bushby, MD2, Hanns Lochmüller, MD2, Piraye Serdaroglu-Oflazer, MD1

1 Department of Neurology, Istanbul University, Faculty of Medicine, Istanbul, Turkey
2 Institute of Human Genetics, Newcastle University, Newcastle upon Tyne, United Kingdom
3 Department of Pneumology, Istanbul University, Faculty of Medicine, Istanbul, Turkey
4 Sisli Etfal Research and Training Hospital, Istanbul, Turkey
5 Department of Neurology, Ege University Medical Faculty, Izmir, Turkey
6 Department of Histology and Embryology, Istanbul University, Faculty of Medicine, Istanbul, Turkey
7 Department of Molecular Genetics and Diagnostics, NIEH, Budapest, Hungary

Correspondence to: Prof. Dr. Piraye Serdaroglu-Oflazer,
Department of Neurology, Istanbul University, Istanbul Faculty of Medicine,
34390, Capa, Istanbul, TURKEY
E-mail: pirayes@istanbul.edu.tr

Key words: Oculopharyngodistal myopathy, hereditary, distal, rimmed vacuole

Total number of words in the text: 2998
Total number of words in the abstract: 250
The character count of the title: 96
Number of references, tables, and figures: 297, 2, 3
**Study funding:** This work was supported by the American Academy of Neurology through an International Scholarship Award to HD, by the European Neurological Society (ENS) through a fellowship to HD, by Science City Newcastle, by the Medical Research Council (MRC) through the Centre for Neuromuscular Diseases, and by the Association Francaise contes les Myopathies (AFM, France). Newcastle University is the coordinating partner of the TREAT-NMD network of excellence (EC 036825).
The Financial Disclosure Statement:

This study supported by Science City Newcastle, by the Medical Research Council (MRC) through the Centre for Neuromuscular Diseases, and by the Association Francaise contes les Myopathies (AFM, France). Newcastle University is the coordinating partner of the TREAT-NMD network of excellence (EC 036825)

Dr Hacer Durmus received International Scholarship Award from American Academy of Neurology and is supported by the European Neurological Society (ENS) through a fellowship.

Dr Steve H. Laval reports no disclosures.

Dr Feza Deymeer reports no disclosures.

Dr Yesim Parman reports no disclosures.

Dr Esen Kiyan reports no disclosures.

Dr Munevver Gokyigit reports no disclosures.

Dr Cumhur Ertekin reports no disclosures.

Dr Ibrahim Ercan reports no disclosures.

Dr Seyhun Solakoglu reports no disclosures.

Dr. Veronika Karcagi reports no disclosures.

Dr Volker Straub reports no disclosures.

Dr Kate Bushby reports no disclosures.

Dr Hanns Lochmüller reports no disclosures.

Dr Piraye Serdaroglu-Oflazer reports no disclosures.
ABSTRACT:

Background: Oculopharyngodistal myopathy (OPDM) has been reported as a rare, adult-onset hereditary muscle disease with putative autosomal-dominant and -recessive inheritance. OPDM patients present with progressive ocular, pharyngeal and distal limb muscle involvement. The genetic defect causing OPDM has not been elucidated so far.

Patients and Methods: Clinical and genetic findings of 47 patients from nine unrelated Turkish families diagnosed with OPDM at the Department of Neurology, Istanbul Faculty of Medicine between 1982 and 2009 were evaluated.

Results: The mean age of onset was around 22 years. Both autosomal-dominant and -recessive traits were observed, without any clear difference in clinical phenotype or severity. The most common initial symptom was ptosis, followed by oropharyngeal symptoms and distal weakness which started after the 5th disease year. Intrafamilial variability of disease phenotype and severity was notable in the largest AD family. Atypical presentations, such as absence of limb weakness in long term follow-up in nine, proximal predominant weakness in four and asymmetric ptosis in three patients were observed. Swallowing difficulty was due to oropharyngeal dysphagia with myopathic origin. Serum creatine kinase levels were slightly increased and electromyography revealed myopathic pattern with occasional myotonic discharges. Myopathological findings included rimmed and autophagic vacuoles and chronic myopathic changes. Importantly, considerable proportion of patients developed respiratory muscle weakness while still ambulant. Linkage to the genetic loci for all known muscular dystrophies, and for distal and myofibrillar myopathies was excluded in the largest AD and AR OPDM families.

Conclusions: We suggest that OPDM is a clinically and genetically distinct myopathy.
Introduction

Oculopharyngodistal myopathy (OPDM) is a rare, adult-onset hereditary muscle disease with both autosomal-dominant and -recessive inheritance patterns\(^1,2\). So far, a total of twenty-nine patients from fourteen families presenting a clinical phenotype compatible with the original report have been described world-wide\(^1,2,3,4,5,6,7,8,9,10,11\). Patients with OPDM have been reported to show symmetric ptosis and ophthalmoparesis and to develop swallowing difficulties and distal muscle weakness\(^8\). Muscle histochemistry shows myopathic changes of different severity with rimmed vacuole formation\(^9\). The genetic defect causing OPDM has not been identified so far.

Here we describe our detailed clinical and molecular genetic findings in 47 patients with OPDM from Turkey. The considerable size of the cohort studied and the long term follow-up enables us to further define the phenotypic characteristics and the temporal course of the condition. Our cohort includes a large spectrum of patients with early and late clinical features of OPDM, as well as patients with atypical presentations.
Patients and methods

Clinical and laboratory findings of forty-seven patients from nine unrelated Turkish families diagnosed with OPDM at the Department of Neurology, Istanbul Faculty of Medicine between 1982 and 2009 were evaluated. Patients who had the clinical phenotype and muscle biopsy findings compatible with the previous reports on OPDM were identified and first degree family members of the patients showing oculopharyngeal involvement with or without limb weakness were included in the study. After reviewing the records retrospectively, neurological re-examination of the living patients was performed by two of the authors (H.D. and P.S-O.). Clinical data of ten other deceased patients were obtained from relatives and clinic charts. Written informed consent of all participants (or guardians of patients) was obtained according to the Declaration of Helsinki, and the study was approved by the Ethical Committee of Istanbul University Faculty of Medicine.

Diagnostic electrophysiological studies included standard electromyography (EMG) and nerve conduction studies (NCV). Further electrophysiological studies for the evaluation of swallowing were performed by two of the authors (C.E. and M.G). The degree of dysphagia was compared with the electrophysiological findings using a previously described grading system12. Piecemeal deglutition and dysphagia limit assessment using 3, 5, 10, 15 and 20ml bouts of water13 and percutaneous electromyography on thyroarythenoid (TA) and cricopharyngeal (CP) sphincter muscles were performed.

Otolaryngological examination, including evaluation of vocal cords’ alignment and function, voice, articulation, swallowing was performed by one of the co-authors (I.E.).

Skeletal muscle biopsies were performed in at least one index patient from each family. Eight μm sections from shock-frozen tissue samples were stained with haematoxylin-eosin (H&E), modified Gomori’s trichrome (MGT), acid phosphatase, periodic acid-Schiff (PAS), NADH dehydrogenase (NADH-TR), succinate dehydrogenase (SDH), cytochrome c oxidase (COX), and oil red O (ORO) using standard procedures. Electron microscopy was performed in three patients.

Spirometric measurements including forced vital capacity (FVC) in sitting and supine position, forced expiratory volume in 1 second (FEV1), FEV1/FVC ratio and day-time arterial blood gas measurements were performed by one of the co-authors (E.K.). The lips of the patient were manually pressed against the mouth piece to prevent air leakage if necessary. Echo- and electro-cardiographic evaluations were done at different cardiology clinics following standard protocols.

For exclusion of OPMD, at least one patient for each family was analyzed for GCG expansion in exon 1 of the \textit{PABPN1} gene. PCR testing essentially followed the published protocol, but used a new reverse primer (3′TCAGACTCCAGGCCGTTC) 14. Myotonic dystrophy 1 was excluded by screening the CTG-repeat in the 3’ region of the dystrophia myotonica-protein kinase (\textit{DMPK}) gene with triplet repeat primed-PCR. Five patients were analyzed for FSHD by direct genetic testing using probe p13E-11.
Thirty-six individuals (fifteen from family 1, three from family 2, five from family 3, four from family 4, two from families 5, 6, 7, 8 and one from family 9) were selected and genotyped using the Illumina Infinium II Human Linkage-12 Panel which includes 6,090 validated SNP markers by GeneService Ltd, Nottingham. We performed multipoint parametric and non-parametric linkage analysis on the largest autosomal-dominant (Family 1) and autosomal recessive (Family 2) families separately and combined with other families using Merlin. Autosomal recessive, autosomal-dominant, and co-dominant disease models were used for the parametric linkage analyses. The linkage was considered as excluded if the LOD score was less than -2 (not shown in the table).
Results

Clinical findings:

Sixteen patients were women and thirty-one were men (table 1). Inheritance was compatible with autosomal-dominant trait in five families with a total of thirty-five patients (family 1, 3, 4, 6, 8) and was suggestive of autosomal recessive trait in one family (family 2) including five patients. The pattern of inheritance could not be determined with confidence in three families (family five, seven and nine; figure 1). The mean age of onset was 22.1 ± 8.5 years (ranging from 7 to 50 years). The mean disease duration was 17.2 ± 12.3 years (range between 1 and 41 years) at the time of the last examination. The mean follow-up period was 39.4 months (ranging between 5 months and 17 years).

The most common initial complaint was droopy eyelids (36/47) (table 1). Forty-six patients had ptosis which was accompanied with variable degrees of ophthalmoparesis in thirty-nine (table 1). These were the only symptoms in patients with disease duration less than five years. Lateral gaze was usually affected first and most severely. The ptosis was asymmetric in four patients and one (patient 35) of them also had asymmetric extremity weakness.

Facial muscle wasting was seen in thirty-six patients (figure 2, figure E-1) with disease duration more than five years, the most severely affected being orbicularis oris, malar, and zygomatic muscles. Sternoclidomastoideus muscle weakness was not found until advanced stages of the disease.

Thirty-four patients with disease duration more than five years showed slowly progressive weakness which initially affected the distal muscles (figure 2). Sixteen of these thirty-four patients developed proximal muscle involvement during the course of the disease. Three of the seven patients who were examined at an early stage of the disease showed weakness of finger and toe extensors, four (patient 9, 10, 45 and 46) showed mild medial gastrocnemius muscle atrophy and mild tibialis anterior muscle weakness. Four other patients (patients 8, 38, 39, 41) had clearly dominant proximal weakness with proximal onset, especially in the lower extremities (table 1 and table E-1). Nine patients between ages 8 to 75 years and with disease duration of 18.3 ± 26.5 years (ranging between 1 and 55 years) had no skeletal muscle weakness at the time of the examination. Three patients were wheelchair-bound at fifteen, twenty-one and twenty-seven years after the disease onset.

Swallowing difficulty, which was the major complaint of patients with disease duration more than five years, was present in thirty-five and laryngeal involvement with hoarse and nasal voice in thirty patients. Dysphagia was more pronounced for fluids and nineteen patients lost weight in excess of 10 kg during the course of the disease. Three patients (patients 29, 31 and 44) had undergone cricopharyngeal myotomy because of severe progressive dysphagia, without clinical benefit in any. Mild to severe tongue weakness was found in twenty-two and high palate in twenty-six patients. Seven of the thirteen patients who underwent ENT examination had bowing of the vocal cords. Patients 21 and 45 had sensorineural hearing loss and three other patients complained of reduced hearing (patients 14, 31, 38).
Ten patients died during the follow-up at the mean age of 44.2 ± 19.8 years (range between 29 and 75 years). Six of them died due to disease-related causes (mean age at the time of death 40.2 ±18.5) such as aspiration pneumonia, disease duration was 18.5 ±3.6 years (ranging from 15 to 24 years), at the time of death. The cause of death was unknown in three patients.

**Laboratory findings:**

Routine laboratory tests were within normal limits. Serum creatine kinase levels were measured in 15 patients and varied from normal values to eight fold of the upper limits (table 1).

All sixteen patients who underwent routine electrophysiological studies revealed normal NCVs -except for patient 41, who had concomitant demyelinating neuropathy- and myogenic motor unit potentials with myotonic discharges in both proximal and distal muscles in eight (table E-2). The discharges had waxing and waning characteristics (in both amplitude and frequency) typical for myotonic discharges.

Electrophysiological evaluation of swallowing of fifteen patients revealed abnormal dysphagia limit during swallowing of a 3-5ml water bolus in ten (patient 14, 15, 16, 20, 23, 24, 27, 31, 36, and 39). This was interpreted as oral and upper pharyngeal involvement. Needle EMG of thyroarythenoid (TA) and cricopharyngeal (CP) sphincter muscles was performed in five patients with severe dysphagia and showed pure myopathic changes in TA in four (patient 14, 15, 31, 36), with no myotonic discharges in TA and CP-sphincter muscles investigated.

Spirometry was performed in twenty-one patients who were independently ambulant except three who were walking with support and one who was wheel-chair bound. Clinical and laboratory findings of thirteen of them revealed respiratory involvement of differing severity, starting from the sixth year of onset. FEV1/FVC ratio was ≥80% in all patients. Mild-moderate (n=5) (FVC between 50-70%) to severe (n=2) (FVC <50%) restrictive ventilatory defect was found in seven patients. Postural drop in FVC of more than 10% indicating diaphragmatic weakness observed in seven patients (table E-2). Eight patients (patients 16, 15, 21, 31, 32, 37, 38, 39) had daytime hypercapnia (pCO2>45 mmHg in arterial blood gas measurement). Three patients required nocturnal non-invasive positive pressure ventilation (BiPAP) 21, 29 and 41 years after disease onset.

Echo- and electro-cardiographic evaluations were normal in eight investigated patients.

Skeletal muscle biopsies performed in twelve patients at different stages of the disease revealed myopathic changes with rimmed vacuoles in all (figure 3A, B, C). Chronic myopathic changes without any myonecrosis and inflammation were the most consistent finding. Electron microscopy of the muscle biopsy of patients 6, 20, 42 revealed several autophagic vacuoles containing various multilamellar structures with mixtures of glycogen granules, myelin and finger-print-like concentric whirlly figures, granular and fibrillar material (figure 3D).

**Molecular genetic studies**
Amplification of exon-1 of PABPN1 to search for GCG expansion to exclude OPMD and exclusion of locus of PABPN1 gene based on LOD scores lower than -2.0 in linkage analysis (LOD score was -3.7 on AD model, -2.8 on AR model) excluded OPMD for all patients tested (at least one patient for each family). All the tested patients showed normal CAG repeats in the DMPK gene excluding DM1. Five patients were analyzed for FSHD by direct genetic testing using probe p13E-11. Three of them showed showed an EcoRI/BlnI fragment size of ≥38 kb on Southern blot, thus suggesting normal D4Z4 repeat number on 4q35. Two samples had lower EcoRI fragment sizes than the pathogenic limit of 38 kb but both were BlnI sensitive suggesting 10q26 origin of the fragments27, 28. Therefore, in all cases FSHD could be excluded. The genetic loci for all known muscular dystrophies, distal and myofibrillar myopathies (ZNF9,PABPN1, LMNA, SYNE1, SYNE2, MYOT, CAV3, CAPN3, DYSF, SGCG, SGCB, SGCA, SGCD, TCAP, TRIM32, FKRP, TTN, POMT1, POMT2, ANO5, POMGNT1, FKTN, LAMA2, FCMD, LARGE, SEPN1, DNM2, COL6A1, COL6A 2, COL6A 3, ITGA7, PLEC1, GDF8, DYSF, DES, TTN, GNE, MYH7, NEB, ZASP, LDB3, TPM3, TPM2, CRYAB, SEPN1, FLNC, BAG3, ACTA1, TNNT1, CFL2, MTM1, MYH7, CNTN1, LAMP2, DMPK, VCP, MYHC2A, MATR3) were excluded in the largest autosomal-dominant and autosomal recessive OPDM families (Family 1 and 2) based on LOD scores lower than -2.016.
Discussion

Since its acknowledgement as OPDM in 1977, twenty-nine patients from fourteen families with a rare, hereditary, adult onset myopathy having ocular, pharyngeal and distal extremity involvement were presented in ten reports from different parts of the world. Oculopharyngeal muscular dystrophy (OPMD) was genetically excluded in only seven of these families. Here we report the largest series of forty-seven patients with OPDM from Turkey. In our OPDM families, DM1, FSHD and OPMD were excluded genetically by direct testing. Furthermore, linkage analysis convincingly excluded chromosomal loci for all known adult-onset muscle disorders with ocular or distal involvement in our largest putative autosomal-dominant and autosomal-recessive families.

The mean age of onset in our group was slightly earlier than in the published series. This may be due to a different genetic defect causing OPDM phenotype in the Turkish patients. Alternatively, multi-generational knowledge about the condition in the Turkish families may have led to early recognition by patients and relatives. In our largest OPDM family (family 1) with nineteen affected patients, symptoms became apparent ten years earlier in the 3rd generation than in the 2nd generation. Significant variation in the age of onset, severity and distribution of weakness among the affected close relatives in this family may suggest anticipation (Table 2).

Both autosomal-dominant and autosomal-recessive inheritance patterns were present in our families. Thirty-six (family 1, 3, 4, 6, 8) of the forty-seven patients came from Kastamonu, a town located in the North-West of Turkey, whereas the other families originated from different regions of the country. Notably, all OPDM families from Kastamonu were compatible with autosomal-dominant inheritance. Patients from autosomal-dominant and autosomal-recessive families did not show a significant difference for age of onset, clinical presentation, disease severity and laboratory findings. Despite these similarities, different causative genes need to be considered based on the different inheritance patterns. Coincidental occurrence of various mutations in OPDM is still possible, but similar onset, clinical course and laboratory findings in all patients renders this possibility unlikely. Different repeat size in trinucleotide repeat disorders could also cause both seemingly autosomal-dominant and autosomal-recessive inheritance patterns. In addition to an AR inheritance, other mechanisms such as germline mosaicism or a premutation in one of the parents may also be considered in family two. The inheritance pattern might be autosomal recessive in family five, seven and nine, but X-linked inheritance cannot fully be ruled out in some of the smaller families.

Although ptosis was the most frequent initial symptom in agreement with previous studies, prominent facial muscle atrophy was the most stigmatizing finding. Previously not reported findings such as mild to moderate asymmetrical ptosis in four of our patients with asymmetrical extremity
weakness in one, and the presence of prominent proximal weakness in four other patients widen the clinical spectrum of OPDM.

Oropharyngeal dysphagia of myopathic origin was one of the most prominent features of the condition. Experience in interventional procedures such as cricopharyngeal myotomy in OPDM is limited. As three of our patients who had undergone this procedure experienced worsening in swallowing thereafter, it is recommended to be used with caution. Botulinum toxin injection is likewise not recommended. Physiotherapeutic conditioning of the buccal and pharyngeal muscles and percutaneous endoscopic gastrostomy (PEG) placement in patients with weight loss or frequent aspiration should be considered early in the course of the disease.

Seven of the thirteen patients who underwent ENT examination had bowing of vocal cords, which refers to the existence of a gap between the vocal cords during phonation that is caused by loss of vocal cord volume. Disproportional bowing without impairment of mobility of vocal cords might have contributed to hoarseness, dysphagia predominantly with fluids, and to aspiration. Five of our patients complained of hearing loss, two of whom had findings of sensorineural hearing loss, suggesting that the sensorineural hearing loss may be a feature of the disease.

Respiratory muscle involvement has previously been reported in four patients with OPDM. Although respiratory involvement is a common finding in the late stage of several myopathies, early respiratory involvement is relatively rare except for a few examples such as Pompe’s disease, rigid spine syndrome and distal myopathy with early respiratory failure. Early respiratory involvement (restrictive ventilatory defect, daytime hypercapnia or diaphragmatic weakness) while the patients were still ambulant was a frequent finding in our patients. Respiratory complications were also frequent and major causes of death in our cohort. Early and regular assessment of respiratory function is therefore highly recommended. Non-invasive positive pressure ventilation should be advocated for treating nocturnal hypoventilation and respiratory failure, and for preventing secondary complications such as pneumonia.

Eight of the sixteen patients who underwent routine EMG had typical myotonic discharges without any clinical sign or symptom of myotonia (table 1). Myotonic discharges in OPDM have rarely been reported by others. Electrical myotonia may be missed if not searched for. Therefore, it is possible that this finding is even more common than has been reported in both our and the previously reported patients and might cause differential diagnostic problems.

Rimmed vacuoles are also found in OPMD, inclusion body myositis, hereditary inclusion body myopathies and several distal myopathies including myofibrillar myopathies. The electron microscopy analysis in three of our patients did not show any tubulo-filamentous inclusions but showed autophagic vacuoles and degradation products (figure 3B).

The attempt to group the clinical findings in our cohort at five years intervals of disease duration at their last visit clearly shows that while there were no other symptoms than ptosis and
ophthalmoparesis in the first five years, facial atrophy, swallowing and speech difficulties, extremity weakness became apparent between five and ten years after onset and gradually worsened thereafter. Respiratory involvement was found in patients with as early as sixth disease year. Therefore, the term “oculopharyngodistal myopathy” may be a rather incomplete description of the condition. “Faciooculolaryngopharyngeal myopathy with distal and respiratory involvement”, acronym being FOLP-DR, maybe a more accurate and descriptive term.

As the genetic defect underlying OPDM is not known yet, the diagnosis currently rests upon clinical and histopathological features, and on the genetic exclusion of similar conditions, namely OPMD, DM1, FSHD and distal myopathies.

There is clinical overlap between OPDM and OPMD as both diseases have similar distribution of weakness and histopathological features. However, onset after 40 years of age is atypical in OPDM. Although both diseases present with progressive ptosis, findings such as limitation of eye movements, facial weakness, distal wasting and weakness are typical for OPDM whereas they are not features of OPMD. Despite these differences, OPDM patients must be carefully screened for OPMD.

Differential diagnosis with DM1 which has involvement of facial and distal limb muscles, together with the presence of electrophysiological myotonia, and with facioscapulohumeral dystrophy (FSHD) which presents with facial atrophy in a young adult patient may be difficult. However, marked ophthalmoparesis is not a feature of any of these diseases and lower facial atrophy in OPDM does not resemble that in FSHD. Similarly, the diagnostic dilemma caused by the distal weakness and wasting present both in the majority of OPDM patients and in other distal myopathies with rimmed vacuoles may be eliminated by considering the prominent ocular, facial and pharyngeal involvement in OPDM.

The present study with an unprecedented number and long follow-up of OPDM patients allowed us to refine the clinical phenotype of OPDM, to propose a more descriptive name for the condition and to pave the way to identify the genetic defect.
Legends for figures:

**Figure 1:** Pedigrees of nine Turkish OPDM families

**Figure 2:** Progression of facial muscle wasting and severe distal atrophy in a patient (12.I/8) from a large AD family. (A) At 16 years of age, note bilateral mild ptosis as the initial symptom. (B) At 20 years of age, ptosis and facial atrophy. (C, D, E) At the age of 43 years, severe facial and distal muscle atrophy in arms and legs (disease duration 27 years).

**Figure 3:** Histological and ultrastructural findings in OPDM. (A and B) Haematoxylin and eosin staining demonstrates myopathic changes in OPDM. Fibre size variation and rimmed vacuoles are marked. (A) Patient 6.I/11, biopsy from the tibialis anterior muscle: Note rimmed vacuoles (arrow) in polygonal or small angular muscle fibres. (B) Patient 22.III/2: Note the rimmed foamy vacuoles. (C) Patient 28.V/3, biopsy from the right biceps muscle: Modified Gomori trichrome demonstrates red-rimmed vacuoles. Vacuoles may be in large or small fibres. (D) Patient 6.I/11, biopsy from the tibialis anterior muscle: Electron microscopy of autophagic vacuoles containing various multilamellar structures with mixtures of glycogen granules, myelin and finger print-like concentric whirlly figures, granular and fibrillar material

**Figure 1e:** Marked facial atrophy, ptosis and incomplete ophthalmoplegia in a 38 year old patient (17.II/2) from a large AR family. (A-E) Note that the most severely affected facial muscles are orbicularis oris, malar, and zygomatic muscles. (A) Neutral position, (D) eyes closed and whistling, (B) right gaze, (C) left gaze, (E) up-ward gaze, (F) down-ward gaze.

Acknowledgements

We are grateful to the patients and their relatives for their participation in the study. We thank Dr. Debbie Hicks, Dr. Tuomo Polvikoski, Dr. Anna Sarkozy (Newcastle upon Tyne, UK), Dr. Vuslat Yılmaz, Dr Ufuk Memis, Dr Nevin Kuloğlu, Dr Nazli Basak, Ms Hatice Tasli (İstanbul, Turkey) and Dr. Moris Jack Danon (New York, USA) for discussion. CE is an invited scientist of the Turkish Academy of Sciences. This work was supported by the Academy of Neurology through an International Scholarship Award to HD, by the European Neurological Society (ENS) through a fellowship to HD, by Science City Newcastle, by the Medical Research Council (MRC) through the Centre for Neuromuscular Diseases, and by the Association Française contre les Myopathies (AFM, France). Newcastle University is the coordinating partner of the TREAT-NMD network of excellence (EC 036825).
References


8. Minami N, Ikezoe K, Kuroda H, Nakabayashi H, Satoyoshi E, Nonaka I. Oculopharyngodistal myopathy is genetically heterogeneous and most cases are distinct from oculopharyngeal muscular dystrophy, Neuromuscul Disord. 2001 Nov; 11(8): 699-702


### Table 1: Comparative summary of clinical findings of our forty-seven and previously published twenty-three OPDM patients

<table>
<thead>
<tr>
<th>Clinical Findings</th>
<th>Our Patients</th>
<th>Published Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>47</td>
<td>26</td>
</tr>
<tr>
<td>Female to male ratio</td>
<td>16:31</td>
<td>10:16</td>
</tr>
<tr>
<td>Mean age of onset (years)</td>
<td>21.9 ±8.8</td>
<td>34.7±13.2</td>
</tr>
<tr>
<td>Initial symptom:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ptosis</td>
<td>36/47</td>
<td>7/26</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>6/47</td>
<td>3/26</td>
</tr>
<tr>
<td>Oculopharyngeal</td>
<td>0/47</td>
<td>4/26</td>
</tr>
<tr>
<td>Distal weakness</td>
<td>1/47</td>
<td>8/26</td>
</tr>
<tr>
<td>Nasal Speech</td>
<td>2/47</td>
<td>1/26</td>
</tr>
<tr>
<td>Other (muscle weakness, fatigue, tired leg, facial atrophy)</td>
<td>2/47</td>
<td>3/26</td>
</tr>
<tr>
<td>Distribution of extremity weakness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distal&gt;Proximal</td>
<td>35/47</td>
<td>24/24</td>
</tr>
<tr>
<td>Proximal&gt;Distal</td>
<td>4/47</td>
<td>0</td>
</tr>
<tr>
<td>No weakness</td>
<td>9/47</td>
<td>0</td>
</tr>
<tr>
<td>Mean CK increase rate</td>
<td>4 X (range normal to 8 fold)</td>
<td>3.4 X (range normal to 5 fold)</td>
</tr>
<tr>
<td>Cardiac involvement</td>
<td>0/8</td>
<td>2/6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td><strong>Respiratory involvement</strong></td>
<td>13/21</td>
<td>4/4</td>
</tr>
<tr>
<td><strong>EMG pattern</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myopathic</td>
<td>16/16</td>
<td>14/14</td>
</tr>
<tr>
<td>Myotonic discharges</td>
<td>8/16</td>
<td>1/14</td>
</tr>
<tr>
<td><strong>Muscle biopsy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myopathic changes</td>
<td>12/12</td>
<td>19/19</td>
</tr>
<tr>
<td>Rimmed vacuoles</td>
<td>12/12</td>
<td>13/19</td>
</tr>
</tbody>
</table>

*Excludes Jaspar 1997 and Witoonpanich 2004*
Table 2: Clinical findings of 19 patients from family 1: Note intrafamilial variability of disease phenotype and severity and note atypical presentation, like patients without weakness in long term disease, proximal predominant weakness and asymmetric ptosis.

<table>
<thead>
<tr>
<th>Patient no.- pedigree no.</th>
<th>Current Age (years)</th>
<th>Sex</th>
<th>Age of Onset</th>
<th>Generation</th>
<th>Initial Symptom</th>
<th>Ptosis</th>
<th>Ophthalo- paresis</th>
<th>Dysphagia and nasal speech</th>
<th>Facial Atrophy</th>
<th>Distribution Of Weakness</th>
<th>Additional Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Family 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-1/1</td>
<td>□ 75</td>
<td>M</td>
<td>50</td>
<td>1</td>
<td>Ptosis</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>No weakness</td>
<td>Unknown cause of death</td>
</tr>
<tr>
<td>2-1/2</td>
<td>□ 50</td>
<td>F</td>
<td>26</td>
<td>2</td>
<td>Dysphagia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>D&gt;P, wheelchair bound at the age of 47</td>
<td>Frequent pneumonia, respiratory failure, exitus at the age 50</td>
</tr>
<tr>
<td>3-1/3</td>
<td>□ 35</td>
<td>M</td>
<td>24</td>
<td>2</td>
<td>Ptosis</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Mild distal weakness</td>
<td>Aspiration pneumonia, exitus at the age 35</td>
</tr>
<tr>
<td>4- 1/4</td>
<td>69</td>
<td>M</td>
<td>Childhood</td>
<td>2</td>
<td>Ptosis</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>No weakness</td>
<td>Pseudo- hypertrophy of gastrocnemius</td>
</tr>
<tr>
<td>5-1/5</td>
<td>□ 50</td>
<td>M</td>
<td>?</td>
<td>2</td>
<td>Ptosis</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Distal, walks independently</td>
<td>Unknown cause of death</td>
</tr>
<tr>
<td>6- 1/6</td>
<td>68</td>
<td>M</td>
<td>?</td>
<td>2</td>
<td>Ptosis</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>No weakness</td>
<td>Pseudohypertrophy of gastrocnemius</td>
</tr>
<tr>
<td>7-1/7</td>
<td>□ 37</td>
<td>M</td>
<td>20</td>
<td>2</td>
<td>Ptosis</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>D&gt;P, wheelchair bound at the age of 35</td>
<td>Respiratory failure, exitus at the age 37</td>
</tr>
<tr>
<td>8- 1/8</td>
<td>56</td>
<td>F</td>
<td>30</td>
<td>2</td>
<td>Ptosis</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+ (mild)</td>
<td>P&gt;D in lower extremities, waddling gait</td>
<td>High palate</td>
</tr>
<tr>
<td>9- 1/9</td>
<td>32</td>
<td>F</td>
<td>20</td>
<td>3</td>
<td>Dysphagia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Distal, walks independently</td>
<td>High palate, Medial gastrocnemius atrophy</td>
</tr>
<tr>
<td>10- 1/10</td>
<td>23</td>
<td>M</td>
<td>?</td>
<td>3</td>
<td>No complaint</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>No weakness</td>
<td>Medial gastrocnemius atrophy (min)</td>
</tr>
<tr>
<td>11- 1/11</td>
<td>42</td>
<td>M</td>
<td>13</td>
<td>3</td>
<td>Ptosis</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>D&gt;P, walks independently</td>
<td>-</td>
</tr>
<tr>
<td>Patient no.-</td>
<td>Pedigree no.</td>
<td>Current Age (years)</td>
<td>Sex</td>
<td>Age of Onset</td>
<td>Generation</td>
<td>Initial Symptom</td>
<td>Ptosis</td>
<td>Ophthalmoparesis</td>
<td>Dysphagia and nasal speech</td>
<td>Facial Atrophy</td>
<td>Distribution Of Weakness</td>
</tr>
<tr>
<td>-------------</td>
<td>-------------</td>
<td>---------------------</td>
<td>-----</td>
<td>-------------</td>
<td>------------</td>
<td>----------------</td>
<td>--------</td>
<td>------------------</td>
<td>-----------------------------</td>
<td>---------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>12-1/12</td>
<td>43</td>
<td>M</td>
<td>16</td>
<td>3</td>
<td>3</td>
<td>Ptosis</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>D&gt;P, walks with support</td>
</tr>
<tr>
<td>13-1/13</td>
<td>40</td>
<td>M</td>
<td>20</td>
<td>3</td>
<td>3</td>
<td>Ptosis</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>D&gt;P, walks independently</td>
</tr>
<tr>
<td>14-1/14</td>
<td>42</td>
<td>M</td>
<td>32</td>
<td>3</td>
<td>3</td>
<td>Ptosis</td>
<td>+</td>
<td>+</td>
<td>+ (mild)</td>
<td>+</td>
<td>Distal, walks independently</td>
</tr>
<tr>
<td>15-1/15</td>
<td>39</td>
<td>F</td>
<td>17</td>
<td>3</td>
<td>3</td>
<td>Ptosis</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>D&gt;P, walks independently</td>
</tr>
<tr>
<td>16-1/16</td>
<td>37</td>
<td>F</td>
<td>21</td>
<td>3</td>
<td>3</td>
<td>Dysphagia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>D&gt;P, walks independently</td>
</tr>
<tr>
<td>17-1/17</td>
<td>34</td>
<td>F</td>
<td>30</td>
<td>3</td>
<td>3</td>
<td>Ptosis</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>D, walks independently</td>
</tr>
<tr>
<td>18-1/18</td>
<td>15</td>
<td>M</td>
<td>15</td>
<td>4</td>
<td>4</td>
<td>Ptosis</td>
<td>+ (min)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>19-1/19</td>
<td>8</td>
<td>M</td>
<td>7</td>
<td>4</td>
<td>4</td>
<td>Ptosis</td>
<td>+</td>
<td>+ (min)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

F=female, M=male, D=distal, P=proximal, ❄️=deceased, min=minimal
Figure 1: Pedigrees of nine Turkish OPDM families

A) Autosomal-dominant families:

B) Autosomal recessive family:

C) The pattern of inheritance could not be determined with confidence in families five, seven, nine