Autosomal dominant progressive external ophthalmoplegia (adPEO) is usually associated with mitochondrial DNA (mtDNA) deletions caused by mutations in nuclear genes involved in mtDNA maintenance, including POLG1 and POLG2, RRM2B, OPA1, ANT3, and PEO1, which encodes an mDNA helicase known as Twinkle.4,5 In these mitochondrial myopathies, adPEO can be isolated or part of a complex clinical syndrome but cannot by itself orient to specific molecular defects. However, if consistent phenotype-genotype correlations could be identified, they might narrow the diagnostic possibilities and even suggest likely genetic causes. We think this may be the case with the especially mild presentations of adPEO due to PEO1 mutations.

Twinkle, a mitochondrial protein similar to bacteriophage T7 primase/helicase, is involved in mitochondrial replication. Published cohorts of patients with autosomal dominant PEO1 mutations showed that ptosis and ophthalmoplegia are the predominant or exclusive clinical features. However, assessment of ocular symptoms, especially ophthalmoplegia, has not always been very accurate and is often limited to defining adPEO as mild or severe.6,7

Of about 100 patients with adPEO and PEO1 mutations, only 3 harbored the p.R357P change6,8 and were less severely affected than recessive patients with mtDNA depletion.9,10 Even when associated with multisystem disorders, adPEO due to PEO1 mutations4,11 was considered relatively benign. However, to our knowledge, there are no data about long-term progression, which are necessary to define the evolution of this disease.

Herein, we report a 16-year clinical follow-up of an Irish-American family with adPEO and the p.R357P PEO1 mutation.
for follow-up studies, we compared photographs taken during the first and second visits.

At recruitment (mean age, 50.6 years; range, 40-57 years), 4 of 9 patients showed ptosis, while only 2 had ophthalmoparesis. At that point, 6 of 9 mutation carriers had no complaints, although 1 showed mild asymmetric ptosis on examination (Table, eFigure in Supplement).

After 16 years of follow-up (mean age, 67 years; range, 56-74 years), 3 more individuals had developed ptosis, which was the only symptom in 5 patients (Figure 2).

Age at onset ranged from 39 to 64 years (mean, 52.4 years), and the first symptom was always ptosis, symmetric in all but 2 cases. Most patients stated that ptosis had progressed and become severe. In fact, 5 of the 9 carrier patients subjected themselves to blepharoplasty. The mean time from onset to blepharoplasty was 4.8 years (range, 1-11 years). The surgical technique involved resection of the levator muscle or plication of the distal levator muscle aponeurosis. Two of 5 patients who underwent operation needed reintervention (patients III-3 and III-16). The times between onset of ptosis and first blepharoplasty (resection) were 7 and 10 years, respectively, while the times between resection and suspension were 7 and 22 years, respectively, with no need for new eyelid repair at the most recent visit. Without surgery, the eyelids started to cover the pupils and interfere with vision.

Table. Patient’s Clinical Data at Recruitment and After 16 Years of Follow-Up

<table>
<thead>
<tr>
<th>Patient No./ Sex/Age at Recruitment, y</th>
<th>Age at Last Visit, y</th>
<th>First Symptom/Age at Onset, y</th>
<th>Ophthalmoplegia on Examination/Grade</th>
<th>Ptosis on Examination/Age at Eyelid Surgery, y</th>
<th>Weakness, MRC Grade</th>
<th>EQ-5D Score for Health in 2012, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>III-2/M/54</td>
<td>70</td>
<td>Ptosis/63</td>
<td>No</td>
<td>No/no</td>
<td>Yes/no</td>
<td>No</td>
</tr>
<tr>
<td>III-3/F/51</td>
<td>67</td>
<td>Ptosis/39</td>
<td>Upgaze/severe</td>
<td>Upgaze/severe/ lateral gaze/mild</td>
<td>Yes/50</td>
<td>Yes/57</td>
</tr>
<tr>
<td>III-4/M/49</td>
<td>65</td>
<td>Ptosis/57</td>
<td>No</td>
<td>No/No</td>
<td>Yes/63</td>
<td>No</td>
</tr>
<tr>
<td>III-7/F/57</td>
<td>74</td>
<td>Asymptomatic</td>
<td>No</td>
<td>Upgaze/mild</td>
<td>No/No</td>
<td>No</td>
</tr>
<tr>
<td>III-8/F/56</td>
<td>72</td>
<td>Ptosis/64</td>
<td>No</td>
<td>Yes</td>
<td>Yes/66</td>
<td>No</td>
</tr>
<tr>
<td>III-9/M/40</td>
<td>56</td>
<td>Ptosis/55</td>
<td>No</td>
<td>No/No</td>
<td>Yes/No</td>
<td>No</td>
</tr>
<tr>
<td>III-10/F/53</td>
<td>69</td>
<td>Ptosis/43</td>
<td>Lateral gaze/mild</td>
<td>ND (AD)</td>
<td>Yes</td>
<td>Yes*/54</td>
</tr>
<tr>
<td>III-12/M/45</td>
<td>61</td>
<td>Asymptomatic</td>
<td>No</td>
<td>No/No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>III-16/F/51</td>
<td>67</td>
<td>Ptosis/46</td>
<td>No</td>
<td>Yes/50</td>
<td>Yes/60</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; MRC, Medical Research Council; ND, not done.  
* Asymmetric.
Only 2 patients showed ophthalmoparesis without diplopia at recruitment and 1 more at follow-up, although none were aware of a problem. The ophthalmoparesis affected mainly upgaze, with complete palsy in patient III-3 and mild restriction in patient III-7. Lateral gaze was involved to a lesser degree in 2 patients, whose lateral movements were restricted by a few millimeters.

Manual muscle testing demonstrated normal strength in all muscles except for mild neck flexion weakness in 2 patients, without overt progression. One patient had weakness of the orbicularis oculi only at the follow-up visit.

At the last visit, 2 patients were still neurologically normal at ages 61 and 73 years.

We used the EQ-5D functional questionnaire to assess activities of daily life, psychological impact of the disease, and general health status as perceived by patients. The descriptive profile yielded top scores for all modalities, and the health state on the visual analog scale ranged between 90% and 100%.

Findings on sensory and motor nerve conduction studies and electromyography were normal, as were serum creatine kinase and venous lactate levels. Funduscopy and optical coherence tomography showed no alterations of the optic nerve or the retina.

A biopsy of the orbicularis oculi performed during blepharoplasty in patient III-3 showed scattered cytochrome oxidase-negative fibers. Biochemical analysis of the respiratory chain showed normal citrate synthase activity and decreased activities of complexes I, III, and IV (15%-30% of normal). Analysis of mtDNA isolated from the orbicularis oculi showed multiple mtDNA deletions both by Southern blot and by long-range polymerase chain reaction.

Discussion

This study describes a 16-year clinical follow-up of a large family with adPEO due to a PEO1 mutation. These patients showed late-onset ocular myopathy with slow and benign progression, beginning with ptosis in all cases. In most of them, ptosis was the only clinical symptom for many years, a feature previously described only in 4 of about 100 described patients with different Twinkle mutations. Although onset was late, once it appeared, ptosis progressed relentlessly and became severe in a few years, leading the patients to seek blepharoplasty on average 4.8 years after onset. Notably, when blepharoplasty consisted of shortening the levator muscle, the ptosis relapsed and a subsequent suspension of the eyelid from the frontalis muscle gave better results. Thus far, no patients who underwent suspension as the first surgery needed a second eyelid repair after 2, 6, and 15 years. We therefore suggest plication of the distal levator muscle aponeurosis as the first option in this disease.

Asymptomatic ophthalmoparesis was revealed by neurological examination only in 3 of the 9 patients. It affected upgaze, whereas lateral gaze was only slightly involved. No further deterioration of extraocular movements was detected during follow-up, showing that the eyelid levator muscle is disproportionately affected in patients with this mutation.

A review of all described patients with mutations in genes involved in adPEO showed that most had multisystemic symptoms (eTable in Supplement) and a minority had only adPEO with ptosis. Three other patients carrying the p.R357P mutation in PEO1 also showed a very benign phenotype. The similar data obtained by us in 9 more patients sup-
port the notion that this among all Twinkle mutations has an especially mild clinical expression. Accordingly, the coexistence of isolated ptosis or very mild adPEO, mitochondrial myopathy, and multiple mtDNA deletions suggests that p.R357P in PEO1 may be the underlying mutation rather than other changes in PEO1 or ANT1. We base this conclusion on the large number of patients and the long follow-up in our family, which is representative of this benign syndrome. Thus, in our experience adPEO due to PEO1 p.R357P mutation is a late-onset ocular myopathy, mostly confined to ptosis, with slow and benign progression, which is important for prognosis and family counseling.

REFERENCES