Secondary Glaucoma in Patients With Familial Amyloidotic Polyneuropathy

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Objective: To elucidate the clinical features and surgical outcomes of the treatment of secondary glaucoma associated with transthyretin (TTR)-related familial amyloidotic polyneuropathy (FAP).

Design: Retrospective case study.

Participants: Forty-nine Japanese patients with FAP.

Methods: For all patients, measurement of best-corrected visual acuity, intraocular pressure, and visual fields as well as slitlamp and ocular fundus examinations were conducted and compared. In addition, the exact mutation of the amyloidogenic TTR variants was analyzed for all 49 patients with FAP. The TTR mutations included amyloidogenic TTR (ATTR) Val30Met in 41 patients, ATTR Tyr114Cys in 6, ATTR Ser50Ile in 1, and a compound heterozygous mutation of ATTR Val30Met + Arg104His in 1.

Results: The onset of secondary glaucoma was defined as elevation of intraocular pressure and glaucomatous changes in visual field defects. Secondary glaucoma was detected in 12 (24%) of the 49 patients. The incidence of secondary glaucoma in patients with the Val30Met mutation (17%) was lower than for the other FAP genotypes (P=.02 using the χ² test). Of 20 glaucomatous eyes, amyloid deposition on the pupil and anterior surface of the lens was found in 18 eyes. Amyloid deposition was found prior to glaucoma in 11 eyes and at the first visit to our clinic in another 7 eyes. In the 11 eyes in which the onset of glaucoma occurred following amyloid deposition on the pupil, mean±SD period between the onsets of pupillary amyloid deposition and glaucoma was 2.55±1.43 years (range, 0.2-4.0 years). Further statistical analyses revealed significant relationships between the onset of secondary glaucoma and both amyloid deposition (P<.001) and vitreous opacity (P<.001). Surgical treatment was required in 15 (75%) of the 20 glaucomatous eyes. In 9 (81%) of the 11 eyes that underwent trabeculectomy, the intraocular pressure was well controlled at or lower than 20 mm Hg during the follow-up period. In the eyes that underwent combined trabeculotomy and sinusotomy (2 eyes), nonpenetrating trabeculectomy (1 eye), or a cyclodestructive procedure (1 eye), the intraocular pressure was poorly controlled.

Conclusions: Glaucoma is not a rare condition in patients with FAP, especially because liver transplantation now enables patients with FAP to live longer. Careful observation of amyloid deposition along the pupil allows the prediction of glaucoma onset.

All patients in this series underwent slitlamp and biomicroscopic examinations to determine the presence of abnormal conjunctival vessels, as in a previous study. The diagnosis of keratoconjunctivitis sicca was made based on the results of the Schirmer test (≤5 mm) and fluorescein (and/or rose bengal) staining. The presence of amyloid deposition on the pupil border or on the anterior surface of the lens (Figure, A and B) and fringed pupil (Figure, C) was also determined. The onset and progression of glaucoma were defined as an elevation in the intraocular pressure (>20 mm Hg) as measured by an applanation tonometer, changes in the optic nerve head appearance, and glaucomatous changes in the visual fields.

### METHODS

We retrospectively examined the clinical records of 49 Japanese patients (20 men and 29 women) with FAP diagnosed and treated from 1987 to 2002. The mean ± SD age of the patients at the first visit to our clinic was 38.6 ± 11.6 years (range, 25-76 years). All patients were referred to the Departments of Internal Medicine, Neurology, and Ophthalmology at Kumamoto University Hospital, Kumamoto, Japan. In all patients, measurement of best-corrected visual acuity, intraocular pressure, and visual fields as well as slitlamp and ocular fundus examinations were conducted at our ophthalmology department. After obtaining informed consent from the patients, surgical treatment and associated examinations were conducted.

For all 49 patients, molecular biological studies were conducted to identify the exact mutation of the amyloidogenic TTR gene and proteins in patients with FAP, the relationship between the clinical features of ocular complications and the different TTR mutations has not previously been determined.

We examined the incidence and clinical features of secondary glaucoma associated with FAP in Japanese patients (Val30Met, Tyr114Cys, Ser50Ile, and a compound heterozygote of ATTR Val30Met + Arg104His). ATTR Val30Met + Arg104His is a double mutation newly found in Japan, one at codon 30 from GTG (valine) to ATG (methionine) and the other at codon 104 from CGC (arginine) to CAC (histidine).

### RESULTS

Of the 49 Japanese patients with FAP, glaucoma was found in 20 eyes of 12 patients (24%). Molecular biological examinations showed Val30Met in 12 eyes of 7 patients, Tyr114Cys in 5 eyes of 3 patients, Ser50Ile in 1 eye of 1 patient, and a compound heterozygote of Val30Met + Arg104His in 2 eyes of 1 patient. In an attempt to elucidate the relationship between TTR mutations and the onset of glaucoma, we excluded the patient with the compound heterozygote from further statistical analysis. Analysis of the 48 patients with a single TTR mutation revealed that the incidence of glaucoma with Val30Met (7/41; 17%) was significantly lower than that with the other mutations (4/7; 57%) (P = .02 using the Fisher exact test) (Table 1).

### OBSERVATION OF OCULAR MANIFESTATIONS

All patients in this series underwent slitlamp and biomicroscopic examinations to determine the presence of abnormal conjunctival vessels, as in a previous study. The diagnosis of keratoconjunctivitis sicca was made based on the results of the Schirmer test (≤5 mm) and fluorescein (and/or rose bengal) staining. The presence of amyloid deposition on the pupil border or on the anterior surface of the lens (Figure, A and B) and fringed pupil (Figure, C) was also determined. The onset and progression of glaucoma were defined as an elevation in the intraocular pressure (>20 mm Hg) as measured by an applanation tonometer, changes in the optic nerve head appearance, and glaucomatous changes in the visual fields.

### PROFILES

Trabeculectomy was performed according to the method described by Cairns. The conjunctiva was incised in a limbal-based manner. In 10 glaucomatous eyes, mitomycin C (MMC) at 0.4 mg/mL for 3 to 5 minutes was used intraoperatively. Combined trabeculectomy and sinusotomy was performed as described previously and is a modification of the procedure by Harms and Dammann. Nonpenetrating trabeculectomy was based on the procedure devised by Zimmerman et al.

### Table 1. Clinical Data for Each Type of FAP

<table>
<thead>
<tr>
<th>Mutation</th>
<th>No. of Patients</th>
<th>Incidence, %</th>
<th>Mean Age at Onset of Systemic Disease, y</th>
<th>No. of Patients With Glaucoma</th>
<th>Incidence of Glaucoma in Each Type of FAP, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Val30Met</td>
<td>41</td>
<td>84</td>
<td>38.4</td>
<td>7</td>
<td>17</td>
</tr>
<tr>
<td>Tyr114Cys</td>
<td>6</td>
<td>13</td>
<td>37.0</td>
<td>3</td>
<td>50</td>
</tr>
<tr>
<td>Ser50Ile</td>
<td>1</td>
<td>2</td>
<td>50</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>Val30Met + Arg104His</td>
<td>1</td>
<td>2</td>
<td>54</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>Total</td>
<td>49</td>
<td></td>
<td>38.8</td>
<td>12</td>
<td>24</td>
</tr>
</tbody>
</table>

Abbreviation: FAP, familial amyloidotic polyneuropathy.
ity (P < .001). On the other hand, there was no statistically significant relationship between the occurrence of glaucoma and abnormal conjunctival vessels, seen in 12 (20%) of the 60 eyes (P = .26), or the occurrence of glaucoma and keratoconjunctivitis sicca, seen in 15 (25%) of the 59 eyes (P = .78) (Table 2).

The mean ± SD follow-up period for the glaucomatous patients in our department was 4.27 ± 4.11 years (range, 0.1-12.0 years). In the 20 glaucomatous eyes, the occurrence of secondary glaucoma was found in both eyes of 8 patients and in 1 eye of 4 patients. The mean ± SD age at onset of glaucoma was 53.1 ± 7.9 years (range, 44-77 years). The mean ± SD period between the onset of systemic abnormalities caused by polyneuropathy and the onset of glaucoma was 7.01 ± 3.25 years (range, 0.5-12.3 years). In these 20 glaucomatous eyes, 18 eyes had amyloid deposition. Amyloid deposition was found prior to glaucoma in 11 eyes and at the first visit to our clinic in another 7 eyes, as indicated in Table 3.

In an attempt to control intraocular pressure, glaucoma surgery was performed for 15 of the 20 glaucomatous eyes (Table 3). Three of these 15 eyes had been operated on at other hospitals before the patients visited our department. In 1 (case 10) of these 3 eyes, cyclodestructive procedures were performed but resulted in visual loss caused by central retinal vein occlusion and subsequent neovascular glaucoma. In the remaining 2 eyes, trabeculectomy with MMC was performed. In one eye (case 8; right eye), neovascular glaucoma due to central retinal vein occlusion occurred, whereas in the other eye (case 12; right eye), an additional cyclodestructive procedure was required to control the intraocular pressure. In 12 of the 15 eyes that underwent surgery at our hospital, the operations performed were as follows: trabeculectomy with or without the intraoperative aid of MMC in 9 eyes (8 eyes with MMC and 1 eye without MMC), combined trabeculotomy and sinusotomy in 2 eyes, and nonpenetrating trabeculectomy in 1 eye. In the remaining 5 of the 20 glaucomatous eyes, in lieu of glaucoma surgery, antiglaucoma medication was prescribed. In 3 of these 5 eyes, although antiglaucoma medication could not maintain the intraocular pressure lower than the 20-mm Hg level with a mean ± SD pressure of 25.0 ± 2.6 mm Hg, we continued our observation and the use of antiglaucoma medication because of the systemic condition and lack of progression of visual field defects. In the other 2 eyes, the intraocular pressure was maintained at less than 20 mm Hg.

The mean ± SD preoperative intraocular pressure was 35.0 ± 9.0 mm Hg. In 10 (83%) of the 12 eyes operated on at our hospital, the intraocular pressure was well controlled at or lower than 20 mm Hg during the follow-up periods (mean ± SD, 1.23 ± 1.79 years; range, 0.2-6.5 years). In all 9 eyes that underwent trabeculectomy, the intraocular pressure was well maintained and

### Table 2. Incidence of Ocular Manifestations of FAP and Glaucoma in Each Manifestation

<table>
<thead>
<tr>
<th>Ocular Symptom</th>
<th>Eyes, No. (%)</th>
<th>Glaucoma in Each Ocular Manifestation, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACV</td>
<td>60 (61)</td>
<td>12 (20)</td>
</tr>
<tr>
<td>KCS</td>
<td>59 (60)</td>
<td>15 (25)</td>
</tr>
<tr>
<td>Vitreous opacity</td>
<td>35 (35)</td>
<td>17 (49)</td>
</tr>
<tr>
<td>Amyloid deposition on the pupil</td>
<td>30 (31)</td>
<td>17 (57)*</td>
</tr>
<tr>
<td>Fringed pupil</td>
<td>8 (8)</td>
<td>8 (100)*</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>20 (20)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ACV, abnormal conjunctival vessel; FAP, familial amyloidotic polyneuropathy; KCS, keratoconjunctivitis sicca.

*P < .001.
Among known ocular complications in FAP, glaucoma is the major cause of vision loss in these patients. In 5 of these 3 patients, glaucoma was found to occur even after liver transplantation. Furthermore, in all 5 glaucomatous eyes, deposition of ocular amyloid on the pupil border was observed. In 3 (25%) of the 12 glaucomatous patients with FAP, liver transplantation was performed for the treatment of systemic abnormalities. In 5 eyes of these 3 patients, glaucoma was found to occur even after liver transplantation. In 4 (80%) of the 5 glaucomatous eyes, amyloid deposition on the pupillary margin occurred after liver transplantation (Table 3).

### Table 3. Clinical Course of Patients With Secondary Glaucoma Due to FAP

<table>
<thead>
<tr>
<th>Case/Sex/ Age at Onset, y</th>
<th>Mutation</th>
<th>Visual Acuity at First Visit</th>
<th>Visual Field Classification at First Visit</th>
<th>Age at Amyloid Deposition on Pupil, y</th>
<th>Age at Onset of Vitreous Opacity, y</th>
<th>Age at Onset of Glaucoma, y</th>
<th>Age at Final Visit, y</th>
<th>IOP Before Surgery, mmHg</th>
<th>IOP at Final Visit, mmHg</th>
<th>Glaucoma Surgery</th>
<th>Age at Final Visit, y</th>
<th>Visual Acuity at Final Visit</th>
<th>IOP at Final Visit, mmHg</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/47 Val30Met</td>
<td>R 20/20</td>
<td>0</td>
<td>+</td>
<td>52</td>
<td>52</td>
<td>52</td>
<td>60</td>
<td>20/30</td>
<td>10</td>
<td>Trabeculectomy (54)</td>
<td>20/200</td>
<td>14</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>2/F/45 Val30Met</td>
<td>R 20/40</td>
<td>5</td>
<td>NA</td>
<td>53</td>
<td>57</td>
<td>21</td>
<td>57</td>
<td>20/40</td>
<td>4</td>
<td>Trabeculectomy with MMC (59)</td>
<td>20/200</td>
<td>11</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>3/F/73 Val30Met</td>
<td>R 20/30</td>
<td>0</td>
<td>NA</td>
<td>76</td>
<td>53</td>
<td>23</td>
<td>79</td>
<td>20/30</td>
<td>12</td>
<td>Trabeculectomy with MMC (57)</td>
<td>20/200</td>
<td>11</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>4/F/38 Val30Met</td>
<td>R 20/20</td>
<td>45</td>
<td>NA</td>
<td>45</td>
<td>45</td>
<td>41</td>
<td>48</td>
<td>20/15</td>
<td>16</td>
<td>Trabeculectomy with MMC (48)</td>
<td>20/50</td>
<td>14</td>
<td>Hypotonic maculopathy</td>
<td></td>
</tr>
<tr>
<td>5/F/36 Val30Met</td>
<td>R 20/20</td>
<td>42</td>
<td>46</td>
<td>NA</td>
<td>43</td>
<td>31</td>
<td>47</td>
<td>20/20</td>
<td>12</td>
<td>Trabeculectomy with MMC (47)</td>
<td>20/15</td>
<td>12</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>6/F/41 Val30Met</td>
<td>R 20/20</td>
<td>49</td>
<td>53</td>
<td>52</td>
<td>54</td>
<td>41</td>
<td>60</td>
<td>20/20</td>
<td>17</td>
<td>Trabeculectomy with MMC (59)</td>
<td>20/20</td>
<td>13</td>
<td>NA</td>
<td></td>
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<tr>
<td>7/F/51 Val30Met</td>
<td>R 20/20</td>
<td>50</td>
<td>51</td>
<td>51</td>
<td>54</td>
<td>37</td>
<td>20/20</td>
<td>13</td>
<td>NA</td>
<td>Trabeculectomy with MMC (51)</td>
<td>20/60</td>
<td>22</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>8/M/43 Tyr114Cys</td>
<td>R 20/40</td>
<td>5</td>
<td>45</td>
<td>47</td>
<td>50</td>
<td>34</td>
<td>53</td>
<td>0</td>
<td>58</td>
<td>Trabeculectomy with MMC (47)</td>
<td>20/40</td>
<td>10</td>
<td>CRVO, NVG</td>
<td></td>
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<tr>
<td>9/F/38 Tyr114Cys</td>
<td>R 20/20</td>
<td>0</td>
<td>45</td>
<td>45</td>
<td>45</td>
<td>42</td>
<td>46</td>
<td>20/40</td>
<td>10</td>
<td>Trabeculectomy with MMC (46)</td>
<td>20/40</td>
<td>10</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>10/F/48 Tyr114Cys</td>
<td>R 20/60</td>
<td>0</td>
<td>42</td>
<td>43</td>
<td>45</td>
<td>43</td>
<td>53</td>
<td>20/20</td>
<td>23</td>
<td>Cyclophotocoagulation (43)</td>
<td>20/20</td>
<td>20</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>11/F/50 Ser500ie</td>
<td>R 20/20</td>
<td>0</td>
<td>43</td>
<td>44</td>
<td>45</td>
<td>32</td>
<td>0</td>
<td>33</td>
<td>33</td>
<td>Cyclophotocoagulation (43)</td>
<td>20/15</td>
<td>10</td>
<td>CRVO, NVG</td>
<td></td>
</tr>
<tr>
<td>12/F/54 Val30Met + Arg1046His</td>
<td>R 20/20</td>
<td>1</td>
<td>56</td>
<td>59</td>
<td>59</td>
<td>56</td>
<td>68</td>
<td>20/30</td>
<td>14</td>
<td>Trabeculectomy with MMC (59)</td>
<td>20/40</td>
<td>9</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CRVO, central retinal vein occlusion; FAP, familial amyloidotic polyneuropathy; HM, hand motions; IOP, intraocular pressure; MMC, mitomycin C; NA, not applicable; NVG, neovascular glaucoma; +, already present at first visit.

*Patient 1 was aged 41 years, patient 6 was aged 47 years, and patient 8 was aged 50 years when liver transplantation was performed. Fringed pupil was found in patients 1, 2, and 7 in both eyes, in patient 3 in the left eye, and in patient 5 in the right eye.

†Determined according to the classification of Aulhorn (modified by Greve).21
Tsukahara and Matsuo\textsuperscript{11} reported the incidence of glaucoma diagnosed in 2 (5.4\%) of 37 patients with FAP, whereas transplantation.\textsuperscript{24-26} Thus, as a result of longer follow-up periods and longer patient life expectancies, the onset and progression of glaucoma have become more frequent and serious ocular complication than previously documented before the advent of transplantation.

Multiple mechanisms seem to be involved in the cause of elevated intraocular pressure in patients with FAP. The deposition of perivasculary amyloid in conjunctival and episcleral tissue may contribute to the elevation in episcleral venous pressure, resulting in an elevation in intraocular pressure.\textsuperscript{11} Another possibility is that the deposition of ocular amyloid leads to a resultant obstruction in the aqueous outflow route.\textsuperscript{27} We believe that the glaucoma associated with FAP is caused by these 2 mechanisms. Although elevation of episcleral venous pressure could not be documented in this study, we were able to detect a relationship between the deposition of ocular amyloid and the occurrence of glaucoma. In our study, we noted the deposition of ocular amyloid at the first examination or before the onset of glaucoma in 18 of 20 glaucomatous eyes. The 2 eyes that had glaucoma without amyloid deposition underwent vitrectomy and lensectomy at another hospital prior to the patients' first consultation with us, and thus the deposition of amyloid may have decreased as a result of those operations. Our results also showed a significant relationship between the onset of glaucoma and pupil abnormalities. The occurrence of glaucoma was confirmed in all 8 eyes with fringed pupils noted in this study. One patient with amyloid deposition developed glaucoma and a fringed pupil almost simultaneously. We hypothesize that the presence of a fringed pupil may be associated with a high amount of amyloid deposition on the pupil border. In addition, in all cases of fringed pupil, conspicuous deposition of ocular amyloid was observed on the pupil margin. Thus, the development of a fringed pupil may indicate the presence of a large amount of ocular amyloid.

In our study, TTR genetic mutation variants included Val30Met in 41 patients, Tyr114Cys in 6 patients, Ser50Ile in 1 patient, and a compound heterozygote of ATTR Val30Met + Arg104His in 1 patient. As previously stated, the Val30Met variant is the most common in Japanese patients. However, the clinical features of FAP in patients with the Val30Met mutation are somewhat different from those seen with other variants. For example, our experience shows that in patients with the Tyr114Cys variant, ocular complications including vitreous opacity will likely occur earlier than the onset of systemic disease and earlier than for patients with the Val30Met mutation.\textsuperscript{28} In this study, the 17\% incidence of glaucoma in patients with the Val30Met variant was significantly lower than the 57\% incidence seen in patients with the other mutations (3 cases with Tyr114Cys, and 1 case with Ser50Ile). Considering the longer life expectancy due to the improvement in systemic treatment, the genetic differences associated with the occurrence of glaucoma may become more significant in the future.

Other ocular manifestations may also predict the onset of this vision-threatening disease. Among the many ocular complications that have been reported, amyloid deposition on the pupil border seems to be the most reliable ocular finding for predicting the onset of glaucoma. The deposition of ocular amyloid is almost always present prior to the onset of glaucoma, occurring several months to years before the diagnosis of glaucoma. Moreover, in our study, the onset of glaucoma was detected in all cases of fringed pupil. Vitreous opacity and pupillary amyloid deposition are highly related to the occurrence of glaucoma. In addition, although a significant association was observed between the occurrence of vitreous opacity and glaucoma, cases of vitreous opacity were not always followed by the onset of glaucoma. These 2 findings may be regarded as 2 different results derived from ocular manifestations of the deposited ocular amyloid. We have noted the progression of ocular manifestations caused by the deposition of amyloid as well as resultant glaucoma even after liver transplantation. This may be caused by the intraocular production of abnormal TTR variants.\textsuperscript{29} In contrast, systemic disorders due to FAP can be treated or addressed, which results in longer life expectancies in these patients.\textsuperscript{29} Thus, early diagnosis and careful treatment of glaucoma associated with FAP are more important than previously thought.

In our results, the intraocular pressure was well controlled and maintained at lower than 20 mm Hg during the follow-up period in 10 (67\%) of the 15 eyes that underwent operations. Unfortunately, our follow-up periods were not long enough to elucidate long-term surgical outcomes because of difficulties in performing follow-up examinations as a result of serious systemic disorders. However, as mentioned previously, because liver transplantation and other systemic treatments presently increase life expectancy, surgical treatment for glaucoma associated with FAP will be required in more patients.

Our experience with the surgical treatment of secondary glaucoma in patients with FAP reveals the application of MMC-augmented trabeculectomy to be the most promising treatment modality. We regard trabeculectomy as a surgical option for the treatment of adult-onset open-angle glaucoma.\textsuperscript{30} Although our experience with trabeculectomy and nonpenetrating surgical procedures is limited, progressive deposition of ocular amyloid even after liver transplantation suggests that obstruction due to the deposited amyloid in the aqueous outflow route (surgically modified trabecular meshwork) can cause failure of the aqueous flow. Thus, at present we recommend MMC trabeculectomy as the primary surgical treatment for secondary glaucoma in patients with FAP.
In conclusion, our study documents the clinical features of secondary glaucoma in patients with FAP. Our results show that glaucoma is not a rare condition in patients with FAP. Careful examination for amyloid deposition along the pupil, as well as fringed pupil, allows the prediction of the onset of glaucoma. This is important because early detection is required to treat this ocular complication.

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