Survival of Patients with Multiple System Atrophy

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We investigated the survival of patients with multiple system atrophy (MSA) in a follow-up study of 59 patients admitted to Nagoya University Hospital between 1976 and 1991. They consisted of 24 patients with olivopontocerebellar atrophy (OPCA), 25 with Shy-Drager syndrome (SDS) and 10 with striatonigral degeneration (SND). The mean age at onset was 54 years, the 3-year survival rate from onset was 90%, and the 6-year survival rate was 54%. Comparison of survival curve by clinical type revealed poorer survival in SDS and SND than in OPCA cases. Although in OPCA, SND and SDS the pathological alterations of the central nervous system are known to be very similar, characterized as MSA, the present study suggests that the earlier and the more severe the involvement of the autonomic nervous system, and to a lesser extent the striatonigral system, the poorer the prognosis may be.

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Key words: prognosis, follow-up study, olivopontocerebellar atrophy, Shy-Drager syndrome, striatonigral degeneration

Introduction

Multiple system atrophy (MSA) is a pathological entity proposed by Graham and Oppenheimer (1). It is now known to include three diseases, which were originally described as different diseases; sporadic olivopontocerebellar atrophy (OPCA) (2), Shy-Drager syndrome (SDS) (3) and striatonigral degeneration (SND) (4). Though the central nervous system (CNS) lesions of OPCA, SDS and SND are pathologically located as the same as in MSA, they clinically have their own specific features besides their commonly shared symptoms (5). Comparative prognosis is considered useful to evaluate the natural course of a given disease. Although the ages at onset, death or duration of illness in each of these three entities have been reported (6–8), there has been no detailed study of survival in MSA patients.

The present retrospective investigation was made to determine whether prognosis differs according to gender, age at onset or clinical type (OPCA, SDS and SND) in MSA, by using the Kaplan-Meier method (9). A more detailed description of the clinical course of MSA would be useful to provide survival information from which the prognosis for an individual patient can be estimated, and to establish a data base for comparative use in therapeutic programs.

Patients and Methods

We reviewed the medical records of 157 patients admitted to Nagoya University Hospital with the diagnoses of either spinocerebellar degeneration, OPCA, SDS, SND or MSA, from 1976 to 1991. Each record was evaluated using the diagnostic criteria proposed by the Research Committee of Ataxic Diseases, the Ministry of Health and Welfare, Japan (Table 1). We excluded patients with evidence of a hereditary trait, good L-dopa response or cerebral vascular disease. Sixty-nine patients (51 males, 18 females) of the 157 patients fulfilled the diagnostic criteria for OPCA, SDS or SND. Fifty-nine of these 69 patients were successfully followed in 1991 either by the medical records or direct contact with the patients themselves or through their family members. Excluding the remaining 10 patients who could not be traced in 1991, we thus examined a total of 59 patients (43 males, 16 females) in the present study.

Two patients had tracheostomy for vocal cord paralysis. We regarded them to be censored at the time of operation. The average length of the follow-up period beginning from the onset of illness was 6 years, ranging from 1 to 13 years. In the assessment of survival, the time of onset was used as the zero point. Since the time of diagnosis is more clearly defined, we also calculated the survival rates from the time of diagnosis.

Survival was assessed by the Kaplan-Meier method, with the logrank test (10) for comparing differences in the survival
Table 1. The Diagnostic Criteria (by the Research Committee of Ataxic Disease, The Ministry of Health and Welfare, Japan, in 1992)

1. Olivopontocerebellar atrophy (OPCA)
   1) Not hereditary. Onset in or after middle age.
   2) Cerebellar ataxia is an initial and cardinal manifestation.
   3) Later, many patients have parkinsonian or autonomic symptoms.
   4) Brain CT and MRI show atrophy of the cerebellum and pons.

2. Shy-Drager Syndrome (SDS)
   1) Not hereditary. Onset in or after middle age.
   2) Progressive autonomic failure is an initial and cardinal manifestation.
   3) Later, some patients have parkinsonian or cerebellar symptoms.
   4) Brain CT and MRI often show atrophy of cerebellum and/or pons.

3. Striatonigral degeneration (SND)
   1) Not hereditary. Onset in or after middle age.
   2) Parkinsonian symptoms are initial and cardinal manifestations.
   3) Later, some patients have autonomic failure and cerebellar ataxia.
   4) Brain CT and MRI often show atrophy of cerebellum.

curve. The survival curve was evaluated by gender, age at onset (comparison of two groups divided by the mean value of the age at onset: i.e., older group ≥ 54 years and younger group < 54 years), and clinical type (comparison between OPCA, SDS and SND).

Results

The age at onset ranged from 38 to 70 years, with a mean of 54 years. There was no significant difference in age at onset by gender.

Table 2 shows the age at onset and duration from onset to diagnosis and clinical features at the time of diagnosis for the three clinical types. Age at onset (mean ± standard deviations) was 55 ± 8, 57 ± 7 and 51 ± 8 years for OPCA, SND and SDS, respectively, without any significant differences. Duration from onset to diagnosis (mean ± standard deviations) was 3 ± 2 years for each type. At the time of diagnosis, cerebellar ataxia, parkinsonism and autonomic failure were observed in 100%, 42% and 92% of 24 OPCA patients, in 40%, 100% and 100% of 10 SND patients, and in 88%, 36% and 100% of 25 SDS patients, respectively. The majority of the patients with MSA, irrespective of their clinical types, had autonomic failure, and in the order of the severity of orthostatic hypotension (OH) and urinary disturbance (UD), they were SDS, SND and OPCA.

At the time of follow-up, 17 of the 59 patients were alive, 42 had died. Figure 1 represents the survival curve from the onset for all patients in the present study: the three-year survival is 90%, and the six-year survival 54%. The corresponding percentages from the time of diagnosis are 48% and 33%, respectively (Table 3).

Figure 2 illustrates the survival curves by gender (43 males, 16 females). In males, the 3- and 6-year survival rate was 90% and 58%, respectively, against 88% and 44% among females. The age at onset had no influence on survival, as shown in Figure 3. In an older group (≥ 54 years at onset), the 3- and 6-year survival rate was 89% and 46%, respectively, against 90% and 61% in a younger group (<54 years).

Survival curves plotted for symptomatologically different onset (OPCA, SND and SDS) showed differences among these clinical types (Fig. 4). The six-year survival with SND and SDS was 47% and 35%, respectively, while the six-year survival for OPCA was 73% (OPCA vs SDS+SND, p<0.01).

Survival rates from the time of diagnosis are shown in Table 3. Like the results calculated from the time of onset, patients with SND or SDS had a poorer prognosis than those with OPCA.

As to the causes of death in 42 patients with MSA (17 OPCA, 5 SND, 20 SDS), 11 patients (3 OPCA, 8 SDS) died suddenly of unknown etiology, 8 patients (4 OPCA, 2 SND, 2 SDS) died of autonomic failure (severe OH or loss of consciousness), 17 died of surgical complications, 2 died of sepsis, and 4 died of congestive heart failure.

Table 2. Clinical Characteristics

<table>
<thead>
<tr>
<th>Type of onset</th>
<th>OPCA</th>
<th>SND</th>
<th>SDS</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>24</td>
<td>10</td>
<td>25</td>
<td>59</td>
</tr>
<tr>
<td>Age at onset (yrs)</td>
<td>55±8</td>
<td>57±7</td>
<td>51±8</td>
<td>54±8</td>
</tr>
<tr>
<td>Duration from onset to diagnosis (yrs)</td>
<td>3±2</td>
<td>3±2</td>
<td>3±2</td>
<td>3±2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical features (at the time of diagnosis)</th>
<th>OPCA</th>
<th>SND</th>
<th>SDS</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebellar ataxia</td>
<td>24 (100%)</td>
<td>4 (40%)</td>
<td>22 (88%)</td>
<td>50 (87%)</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>10 (42%)</td>
<td>10 (100%)</td>
<td>9 (36%)</td>
<td>29 (49%)</td>
</tr>
<tr>
<td>Autonomic failure</td>
<td>22 (92%)</td>
<td>10 (100%)</td>
<td>25 (100%)</td>
<td>57 (97%)</td>
</tr>
<tr>
<td>OH (severe)</td>
<td>2 (8%)</td>
<td>5 (50%)</td>
<td>14 (56%)</td>
<td>21 (36%)</td>
</tr>
<tr>
<td>(mild)</td>
<td>15 (65%)</td>
<td>3 (30%)</td>
<td>10 (40%)</td>
<td>28 (47%)</td>
</tr>
<tr>
<td>UD (severe)</td>
<td>3 (13%)</td>
<td>3 (30%)</td>
<td>14 (56%)</td>
<td>20 (34%)</td>
</tr>
<tr>
<td>(mild)</td>
<td>11 (46%)</td>
<td>2 (20%)</td>
<td>7 (28%)</td>
<td>20 (34%)</td>
</tr>
</tbody>
</table>

a: mean ± SD, b: Number (%), c: OH, orthostatic hypotension, d: OH (severe), severe OH (>50 mmHg; the change in blood pressure between lying and standing position), or loss of consciousness, e: OH (mild), mild OH (>20 mmHg), or orthostatic dizziness, f: UD, Urinary disturbance, g: UD (severe), with incontinence, h: UD (mild), without incontinence.
Survival of Patients with MSA

Fig. 1. Survival curve for all MSA patients. MSA: multiple system atrophy.

Fig. 2. Survival curves for MSA according to gender. Males versus females: not significant.

Fig. 3. Survival curves for MSA according to age at onset. ≥ 54 years versus < 54 years: not significant.

Fig. 4. Survival curves for MSA according to clinical type at onset. OPCA type versus SDS and SND type: significant. OPCA: olivopontocerebellar atrophy, SND: striatonigral degeneration, SDS: Shy-Drager syndrome.

Table 3. Survival Rate of 59 Patients with MSA Calculated from the Time of Diagnosis

<table>
<thead>
<tr>
<th>Type of onset</th>
<th>3-year</th>
<th>6-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPCA</td>
<td>74%</td>
<td>53%</td>
</tr>
<tr>
<td>SND</td>
<td>22%</td>
<td>N.D.*</td>
</tr>
<tr>
<td>SDS</td>
<td>27%</td>
<td>16%</td>
</tr>
<tr>
<td>Total</td>
<td>48%</td>
<td>33%</td>
</tr>
</tbody>
</table>

*N.D.: not determined because of the insufficient follow-up period.

Discussion

We reported the survival of MSA for the first time by using the Kaplan-Meier method. The clinical diagnosis of MSA, consisting of OPCA, SND and SDS, was made in 59 patients who were studied. The mean age at onset in the present study was 54 years, which is compatible with previous reports (6–8). The present study demonstrated that the 3-year survival rate from onset was 90%, and the 6-year survival was 54%. The corresponding percentages from diagnosis were 48% and 33%, respectively. Comparison of the prognosis by survival curve of infections, 2 (1 OPCA, 1 SND) of choking, 1 of malignancy and 1 of suicide. In the other 19 cases, it was impossible to determine the cause of death.
showed a poorer prognosis in patients with SND or SDS than in those with OPCA, but no influences of the age at onset or gender.

The end-stage pathological findings of OPCA, SND and SDS are the same in location for MSA, and these three clinical types are thought to be various manifestations of the same disease (11). The distribution of CNS degeneration is considered to be quite similar in OPCA, SND and SDS. However, the degeneration differs in degree in the cerebellum, basal ganglia and intermediolateral cells in the spinal cord (12, 13), and these three clinical types of MSA have their own distinctive initial manifestations. In the present study, the patients shared the common clinical spectrum of MSA at the time of diagnosis (i.e., cerebellar ataxia, parkinsonism and autonomic failure), but the frequency and severity of these symptoms were different in each clinical type (Table 2) as described in the literatures (5, 12).

The present study demonstrated the prognostic differences among the three clinical types of MSA. The initial and cardinal lesions involved in each patient proved to be important factors. In SDS, for example, an initial and cardinal manifestation is progressive autonomic failure. At the time of diagnosis, fourteen of our patients (56%) with SDS had severe orthostatic hypotension and as many had urinary incontinence (Table 2). Sudden death occurred in eight of 20 patients with SDS, and it could be closely related to the previously reported symptoms of autonomic failure: orthostatic hypotension, postprandial hypotension (14), sleep apnea (15) or vocal cord paralysis (16). Indeed, the vocal cord paralysis observed in patients with MSA is reported to be strongly correlated with the manifestation of urinary incontinence, and to be one of the factors for poor prognosis (16). These observations thus indicated that the possible factor(s) for poor prognosis in SDS patients may be related to severe autonomic nervous system dysfunction.

In SND, the other clinical type of MSA with a poor prognosis, we thought that at least two factors may explain the poor prognosis. First, since the initial and cardinal manifestation of SND is parkinsonism, and since the progression of parkinsonism in the course of SND results in the deterioration of activities of daily living (ADL), the progressive functional impairments in SND may affect the survival prognosis. According to a recent epidemiological study by the Research Committee of Ataxic Diseases in Japan (17), the duration from onset to the end stage (confined to wheelchair or bedridden) is shorter in SND than OPCA (5.2 years) than in OPCA (7.5 years). The present study also showed that orthostatic hypotension and urinary dysfunction were more frequently associated with SND than OPCA (Table 2). Moreover progressive autonomic failure, as in the case of SDS, thus appeared to make for a less favorable survival prognosis in SND than in OPCA. Although autonomic symptoms in OPCA and SND were reported to be not as severe as in SDS (5), the association with autonomic failure, as we reported here, has been more frequently observed in SND than in OPCA (18, 19). However, because of the limited number of patients studied, the exact association of autonomic failure with poor prognosis in SND remains to be determined.

In conclusion, the present study of survival in MSA patients suggests that the earlier and more severe the involvement of the autonomic nervous system, and to a lesser extent the striatogniral system, the poorer the prognosis tends to be. Further population-based studies should be undertaken in order to determine more accurately the clinical features and prognosis in MSA patients.


References
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