The clinical variations of hereditary spastic paraplegia in four families

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The clinical variations of hereditary spastic paraplegia in four families

Davood M. Danadoost, MD,* Charles E. Jackson, MD,** and Robert D. Teasdall, MD*

Hereditary spastic paraplegia was diagnosed in 19 patients belonging to four families. All had spastic gait and upper motor neuron signs in lower limbs. In family A, the disease was expressed in this manner, although one member had muscle wasting in an upper limb. There was additional involvement of the posterior columns in six of the eight affected members of family B and cerebellar ataxia was noted in upper limbs of three of them. Posterior columns were also involved in three of the four affected members of family C. The disease was transmitted in these three families by an autosomal dominant gene. With autosomal recessive inheritance in family C, spastic gait and mental retardation were present during early childhood in the three affected members. Abnormalities of feet, vertebrae and other anomalies were also encountered.

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** Third Medical Division

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*HEREDITARY* spastic paraplegia, first described by Seeligmüller in 1876,1 is primarily a spinal cord disease involving pyramidal tracts and characterized by spastic gait. Although the disease may exist in pure form, ataxia, dementia, extrapyramidal signs, optic atrophy, muscle wasting and posterior column involvement have been described along with skeletal abnormalities.2-7 Recently, we encountered four families in whom the affected members had difficulty walking. In these patients with the diagnosis of hereditary spastic paraplegia, the nervous system involvement was not restricted to the upper motor neuron. Skeletal abnormalities were also observed. Furthermore, the expression of this disease differed between autosomal dominant and recessive forms, between the three families with dominant inheritance and even within members of the same families. Our study presents the spectrum of clinical variations within these families.
Family A

The pedigree of family A is shown in Figure 1. It presents 27 members in six generations. Two members (II-1, III-4) were reported to have difficulty walking and 14 members had gait described as normal. Eleven members were examined. In four, (III-1, III-3, IV-1, V-1) the diagnosis of hereditary spastic paraplegia was made on the basis of spastic gait, brisk deep tendon reflexes in lower limbs and extensor plantar responses. Additional findings in these affected members were wasting of intrinsic hand muscles and pes cavus in III-1, and in V-1 an atrophic upper limb and enlarged thyroid. An enlarged thyroid was also noted in IV-1. The disease was suspected in four younger members (V-3, V-4, V-6, V-7) with normal gait but whose deep tendon reflexes were brisk in lower limbs with flexor plantar responses. Diffuse wasting of an upper limb and hypertrophy of the finger joints were noted in V-6 and the thyroid was enlarged in V-3 and V-4. The remaining three members of this family (V-2, V-5, VI-3) were intact neurologically.

FIGURE 1

PEDIGREE OF FAMILY A

EXAMINED

〇 □ NORMAL
▽ □ SUSPECTED
● □ AFFECTED

NOT EXAMINED (REPORTED)

〇 □ NORMAL
● □ AFFECTED
Spastic paraplegia

neurologically and without other stigmata except for V-2 who had an enlarged thyroid.

In this family the inheritance was compatible with an autosomal dominant mode, although no male to male transmission was noted.

Family B

The pedigree of family B is shown in Figure 2. It presents 55 members in six generations. Five were reported to have difficulty walking (I-1, II-1, III-2, III-4, IV-3) and 36 had gait described as normal. Fourteen members were examined. The diagnosis of hereditary spastic paraplegia was made in eight of these on the basis of spastic gait, brisk deep tendon reflexes in lower limbs and extensor plantar responses (III-1, IV-1, IV-2, IV-4, IV-7, V-2, V-6, V-9). No other abnormal findings were detected in IV-1, and V-9. In the remaining six affected members, the posterior columns were involved and three of these had cerebellar ataxia in the upper limbs (IV-4, V-2, V-6). Posterior column and upper motor neuron involvement were more apparent in the left lower limb of V-6. Scoliosis, lordosis and pes cavus were found in four members (III-1, IV-2, IV-4, V-6). The disease was suspected in three members (V-7, V-8, VI-1) who walked normally with brisk reflexes in lower limbs and flexor plantar responses. In one of these (V-8), minimal involvement of the posterior columns was detected. None was
ataxic and no abnormalities of vertebral columns or feet were detected. Three members (IV-5, IV-6, V-1) of this family walked normally and were found to be normal, except for an equivocal left plantar response in IV-6.

The disease was inherited in an autosomal dominant manner with male to male transmission likely (II-1, III-2). An example of incomplete penetrance is noted in IV-6, who was normal at her present age of 48 years while her son (V-6) was affected at 14.

Family C

The pedigree of family C is shown in Figure 3. Forty-four members in six generations are presented. Difficulty walking was reported in four members (I-1, II-4, III-3, IV-1) and abnormal gait in 20. Among the 20 members of this family examined, four had a diagnosis of hereditary spastic paraplegia (III-4, IV-2, IV-3, V-7). These patients had spastic gait, brisk reflexes in lower limbs and extensor plantar responses. In three of them, (III-4, IV-3, V-7) additional involvement of posterior columns was noted and IV-2 com-

FIGURE 3
PEDIGREE OF FAMILY C

EXAMINED
☐ NORMAL
☑️ SUSPECTED
● AFFECTED

NOT EXAMINED (REPORTED)
☐ NORMAL
● AFFECTED
Spastic paraplegia

explained of painful ankles. The disease was suspected in five members of the fifth generation (V-4, V-6, V-8, V-10, V-11) who had brisk deep tendon reflexes in lower limbs and normal gait except for mild spasticity in V-6. The plantar responses were flexor in these members with suspected disease, except for an equivocal left plantar response in V-4. This member complained of pain in the right knee and foot. Pain in lower limbs was also reported by two other members with suspected disease. Member V-10 mentioned pain in both knees; mild posterior column involvement was detected. Member V-11 said the right knee and hip were painful. The remaining 11 members of this family were found to be neurologically intact.

In this family, the disease was inherited in an autosomal dominant manner with definite male to male transmission (IV-3, V-7). A failure of penetrance was possible in one member (IV-4) since two of her children (V-10, V-11) were suspected of having the disease.

FIGURE 4
PEDIGREE OF FAMILY D

EXAMINED
circle • NORMAL
plus sign □ SUSPECTED
black circle ■ AFFECTED

NOT EXAMINED (REPORTED)
circle ○ NORMAL
diamond ▲ AFFECTED
Family D

The pedigree of family D is presented in Figure 4. It contains 46 members in five generations. Five members of this black family were examined. One member (III-2) was neurologically intact with no defects in mentation noted. She had been separated from her husband (III-1), for several years, but reported that his gait and mentation were normal as were the other members listed in the first three generations. This information was confirmed in a letter received from III-1. In the fourth generation, an 11-year-old member (IV-3) was found on examination to be normal. The diagnosis of hereditary spastic paraplegia was made in three members of this generation (IV-1, IV-9, IV-11). Delayed walking in these patients with spastic gait was noted before age four. The deep tendon reflexes were generally brisk and plantar responses were extensor. No sensory or cerebellar involvement was observed. Severe mental retardation in these affected members from an early age prevented completion of primary school grades. Pes planus was also detected in these patients. The other members of this generation and of the next were reported to be normal.

In this family the mode of inheritance was autosomal recessive.

Table I summarizes the information, presented in the pedigrees, along with the clinical involvement for each family. Table II gives the age of affected members and age of onset as well as the degree of spasticity and other neurological involvement. With the exception of family D, the older patients were more severely incapacitated than the younger members. Note that in successive generations the disease was often discovered at progressively earlier ages.

**Comment**

The initial compliant in the 19 affected patients was difficulty walking. They encountered frequent tripping and clumsiness of

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**TABLE I**

Hereditary Spastic Paraplegia

<table>
<thead>
<tr>
<th>Family</th>
<th>Inheritance</th>
<th>Not Examined</th>
<th>Examined</th>
<th>Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Normal</td>
<td>Affected</td>
<td>Normal</td>
</tr>
<tr>
<td>A</td>
<td>Dominant</td>
<td>14</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>B</td>
<td>Dominant</td>
<td>36</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>C</td>
<td>Dominant</td>
<td>20</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>D</td>
<td>Recessive</td>
<td>41</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

* Suspected: Brisk reflexes in lower limbs with flexor plantar responses, normal gait, except for C V-6.
** Affected: Brisk reflexes in lower limbs with extensor plantar responses, spastic gait.
gait with stiffness and jerking of lower limbs. Knee and ankle jerks were brisk and plantar responses were extensor. On the basis of these upper motor neuron findings confined to lower limbs and family history, the diagnosis of hereditary spastic paraplegia was made. Considerable variation in the degree of weakness and spasticity of lower limbs was observed. The involvement was more severe in the older patients, but only four were bedridden. Difficulty walking was reported in 11 members belonging to families A, B and C. Since these members were not examined, they are excluded from further consideration.

In spite of conspicuous upper motor neuron involvement, flexor and extensor spasms in lower limbs did not occur in these patients with the diagnosis of hereditary spastic paraplegia. Furthermore, they retained normal bladder and bowel functions. Similar findings have been reported in the hereditary spinocerebellar degenerations, including spastic paraplegia. In 13 other patients, the diagnosis of hereditary spastic paraplegia was suspected. The deep tendon reflexes in lower limbs were brisk, yet plantar responses were flexor. All walked normally except for one who had a spastic gait. Bickerstaff has mentioned that the disease should not be suspected solely on the finding of brisk reflexes, while Appel has maintained this criterion is sufficient. Five of our patients support the latter view because they exhibited other stigmata of the disease. The three members of family A suspected of having the disease revealed enlarged thyroid in two of them and high

### TABLE II

**Hereditary Spastic Paraplegia**

<table>
<thead>
<tr>
<th>Pedigree no.</th>
<th>Age of Onset</th>
<th>Degree of Spasticity</th>
<th>Other Neurological Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III-1</td>
<td>69</td>
<td>35</td>
<td>Bedridden (2 yrs.)</td>
</tr>
<tr>
<td>III-3</td>
<td>60</td>
<td>40</td>
<td>Bedridden (9 yrs.)</td>
</tr>
<tr>
<td>IV-1</td>
<td>44</td>
<td>40</td>
<td>Severe</td>
</tr>
<tr>
<td>IV-2</td>
<td>25</td>
<td>21</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lower motor neuron</td>
</tr>
<tr>
<td>Family B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III-1</td>
<td>66</td>
<td>30</td>
<td>Bedridden (6 yrs.)</td>
</tr>
<tr>
<td>IV-1</td>
<td>32</td>
<td>15</td>
<td>Bedridden (2 yrs.)</td>
</tr>
<tr>
<td>IV-2</td>
<td>23</td>
<td>14</td>
<td>Severe</td>
</tr>
<tr>
<td>IV-4</td>
<td>30</td>
<td>19</td>
<td>Severe</td>
</tr>
<tr>
<td>IV-7</td>
<td>34</td>
<td>27</td>
<td>Moderate</td>
</tr>
<tr>
<td>V-2</td>
<td>26</td>
<td>6</td>
<td>Mild</td>
</tr>
<tr>
<td>V-6</td>
<td>22</td>
<td>14</td>
<td>Severe</td>
</tr>
<tr>
<td>V-9</td>
<td>10</td>
<td>8</td>
<td>Mild</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Posterior column</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Posterior column &amp; cerebellum</td>
</tr>
<tr>
<td>Family C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III-4</td>
<td>75</td>
<td>55</td>
<td>Severe</td>
</tr>
<tr>
<td>IV-2</td>
<td>53</td>
<td>51</td>
<td>Severe</td>
</tr>
<tr>
<td>IV-3</td>
<td>35</td>
<td>18</td>
<td>Severe</td>
</tr>
<tr>
<td>V-7</td>
<td>28</td>
<td>20</td>
<td>Mild</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Posterior column</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Posterior column &amp; cerebellum</td>
</tr>
<tr>
<td>Family D</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV-1</td>
<td>17</td>
<td>1 1/2</td>
<td>Severe</td>
</tr>
<tr>
<td>IV-9</td>
<td>25</td>
<td>4</td>
<td>Severe</td>
</tr>
<tr>
<td>IV-11</td>
<td>26</td>
<td>1 1/2</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

**Severe:** assistance required in walking.
**Moderate:** gait spastic and a handicap.
**Mild:** minimal disturbance of gait.
plantar arches along with an atrophic hand in the third. In family C other manifestations of the disease were present in two members. One of these complained of pain in lower limbs, while the posterior columns were involved in the other. Difficulty walking commenced at ages which ranged from 6 to 55 years in 13 patients belonging to three families with dominant inheritance and hereditary spastic paraplegia. The mean age of onset was 28 years. In contrast, the members with suspected disease at the time of examination ranged in age from 8 to 22 years with a mean of 13 years. In view of the younger age of this group with suspected involvement, the disease may not be present in an abortive form, but rather in an early stage of development. Furthermore, the disease probably progresses over many years. The data in Table II suggest an interval as long as 30 years.

Abnormal neurological findings in patients with hereditary spastic paraplegia were not confined to the upper motor neuron. The profound wasting of intrinsic hand muscles in one member of family A was probably due to lower motor neuron disease and a similar lesion might have been responsible for the diffuse wasting in the upper limb of another member of this family. We encountered no other patients with muscle wasting, but lesions of the lower motor neuron have been reported in several families with hereditary spastic paraplegia.9-11

The posterior columns may also be affected in hereditary spastic paraplegia.3 Seven patients in families B and C had posterior column signs which were restricted to lower limbs. This involvement was not a handicap to these patients.

Pure cerebellar ataxia is encountered rarely in families with hereditary spastic paraplegia.2-3 although the family presented by Landau and Gitt12 is probably an example. In contrast, involvement of the cerebellar system and upper motor neuron, termed hereditary spastic ataxia, has been described in a number of families.4,13 This association was noted in three patients belonging to family B whose cerebellar ataxia was demonstrated in upper limbs. Bell and Carmichael8 have stressed the importance of distinguishing hereditary spastic paraplegia from the spastic ataxias. This differentiation was difficult in our patients with cerebellar involvement since their gait was spastic and not ataxic. Furthermore, two members of this family had disease confined to the upper motor neuron.

In the affected members of the three families with dominant inheritance, clinical variations were present not only between families, but different nervous system pathways were involved in members of the same family. As shown in Table II, these clinical variations were not related to age of patients, duration of disease or degree of spasticity. It is interesting to speculate whether this dominantly inherited form of spastic paraplegia is a single entity or whether each represents a discrete disease. Perhaps some biochemical characteristic might be detected which would allow differentiation, as recently reported in Friedreich's ataxia.14

Since familial spastic disorders are encountered rarely in early childhood, the delayed walking with mental retardation in the affected members of family D are of interest. Spastic afflictions have been described in children but in these families, other motor systems became involved and severe mental retardation did not occur.5,15 Dementia commencing in early adult life along with spastic paraplegia and extrapyramidal manifestations has been described in several members of an Amish isolate.16 Only recently have two brothers, products of a consanguineous mating, been reported in whom mental retardation and spasticity were present from infancy.17 Retinitis pigmentosa, optic atrophy and hearing loss were also noted in these infants. Mental deterioration has been described in Friedreich's ataxia, but mentation is usually intact in the other spinocerebellar degenerations, and in hereditary spastic paraplegia.4
Spastic paraplegia

Accordingly, we find unusual the early onset of mental retardation and spasticity without other neurological deficit in the affected members of family C.

Although optic atrophy and retinal degeneration have been reported in patients with hereditary spastic paraplegia, visual impairment was not a complaint in our cases and ophthalmoscopic examination revealed no abnormalities.

Pes cavus and abnormalities of the vertebral column have been noted in hereditary spastic paraplegia and are attributed to the neurological deficit. High arches were encountered in five of our patients with the disease and in four of these, belonging to family B, scoliosis and lordosis were also present. In this family the posterior column involvement might have contributed to these vertebral defects. Similar skeletal abnormalities were not detected in the normal members and were present only in one patient suspected of having the disease. Abnormalities of the vertebral column were not encountered in family C in spite of posterior column involvement. In this family, however, the posterior column signs were not as evident as in family B. The occurrence of pes planus in several affected members of family D is of interest since abnormality of the feet is usually not an accompaniment of spasticity.

In addition, these families had abnormalities other than neurological. The atrophic hand in a patient with hereditary spastic paraplegia, belonging to family A, was quite similar to the developmental abnormalities reported by Cross and McKusick in an Amish family. In family A, several members had an enlarged thyroid. Thyroid function was normal in two of these patients and none exhibited signs of thyrotoxicosis. Joint deformities were also noted in this family and painful joints in lower limbs were a complaint in four members of family C. Although these arthralgias have been attributed to the disturbance of gait, three of these members walked normally.

Hereditary spastic paraplegia is transmitted usually by either an autosomal dominant or recessive gene. On occasion, sex-linked inheritance and sporadic cases have been reported. In three of our families (A, B, and C), the disease was inherited by an autosomal dominant gene while in family D autosomal recessive inheritance occurred. In keeping with the observations of Peter, the recessive form of the disease commenced at an earlier age and progressed more rapidly than the dominant form.

In the three families with dominant inheritance, the disease was discovered at younger ages in successive generations. A similar trend has been noted in other genetic diseases, including hereditary spastic paraplegia. Since the presence of hereditary disease prompts an earlier detection of symptoms and signs in other family members, this probably explains the phenomenon. Furthermore, in families with hereditary spastic paraplegia abnormal neurological findings have been detected in otherwise asymptomatic members.

Acknowledgements:
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References


