Generation of symptomatic palatal tremor is not correlated with inferior olivary hypertrophy

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Summary
Although the generation of symptomatic palatal tremor (SPT) is thought to derive from the abnormal activity of hypertrophic inferior olivary neurones, the actual mechanism of SPT has not yet been elucidated. We therefore investigated the relationship between SPT and the pathological process of inferior olivary hypertrophy (IOH). We examined 16 autopsied subjects with cerebrovascular lesions of the dentate-olivary tracts. We analysed the size of the olives, the number of olivary neurones, synaptic, axonal and astrocytic changes in the olives and the clinical course in the subjects. SPT was observed in eight patients, in seven of whom it appeared 1±2 months after interruption of the afferents then progressed to reach a peak ~1±2 years from the onset. SPT persisted for the rest of the subjects’ lives without decreasing in severity. Neuronal hypertrophic change began 20–30 days after the onset of the causative lesions and reached maximum size, accompanied by prominent astrocytosis and synaptic and axonal remodelling, 6–7 months later. The number of olivary neurones decreased to <10% of that in controls in patients who survived >6 years. Despite the persistence of SPT, both the myelin and the axons of efferent fibres from olivary neurones were severely degenerated in patients who survived several years. Therefore, the appearance of SPT may depend on the hyperactivity of olivary neurones released from inhibitory inputs until the peak of both IOH and SPT. However, the persistence of peak intensity and distribution of established SPT is probably due to both the disturbance of natural rhythmicity in the body and the lack of feedback from the abnormal movement resulting from the dysfunction of the olive.

Keywords: involuntary movement; palatal tremor; olivary hypertrophy; immunohistochemistry

Abbreviations: CVD = cerebrovascular disease; GFAP = glial fibrillary acidic protein; IOH = inferior olivary hypertrophy; ION = inferior olivary nucleus; NF-1 = neurofilament 1; SPT = symptomatic palatal tremor

Introduction
The relationship between the inferior olive and palatal tremor is a classical (Spencer, 1886; Guillain and Mollaret, 1931; Trelles, 1943) but still controversial neurological issue. Palatal tremor, formerly known as palatal myoclonus, has been divided more recently into two forms, essential palatal tremor and symptomatic palatal tremor (SPT) (Deuschl et al., 1990, 1994). SPT appears at intervals ranging from a few weeks to a few months after interruption of the dentate-olivary tract in most cases of inferior olivary hypertrophy (IOH) (Lapresle, 1986). SPT is a rare, 2–3 Hz rhythmic hyperkinesic movement disorder characterized by resistance to internal and external stimulation. The tremulous movement may provoke synchronous contraction of other adjacent cranial muscles and the diaphragm, and may have a remote influence on far distal limb muscles (Nagaoka and Narabayashi, 1984).

On the other hand, IOH is regarded as trans-synaptic degeneration (Cowan, 1970; Duchen, 1992) characterized by neuronal hypertrophy and vacuolation with marked astrocytosis (Gautier and Blackwood, 1961; Sohn and Levine, 1971). Since neurones in the olivary nucleus display autonomous oscillatory firing in the normal condition in which the frequency of their discharge is comparable to that of SPT, it has been believed to be the central pacemaker of SPT (Manor et al., 1997; Llinás, 1984). However, this hypothesis, supporting the role of IOH in the generation of SPT, lacks firm evidence.

The process of neuropathological change that leads to SPT has not been well examined, especially in long-surviving
patients. There has been only a single report that shows the chronology of pathological change of the inferior olives for periods of up to 9.5 months after interruption of the dentate-olivary tract (Goto and Kaneko, 1981). Although the authors divide the degenerative process of IOH into six stages, they do not refer to the development of SPT.

Recent neuroradiological MRI studies have shown that the development of SPT is temporally associated with the appearance of abnormal intensity in the olive and its subsequent enlargement (Yokota et al., 1989; Kitajima et al., 1994; Goyal et al., 2000). To clarify the clinicopathological correlation between SPT and IOH, we analysed the size of the olives, the number of olivary neurones and synaptic, axonal, and astrocytic changes in the olives in 16 autopsied subjects, eight of whom developed SPT.

Material and methods
Sixteen subjects were selected from 494 who had been autopsied at our institute between 1980 and 1996. All subjects had suffered primary cerebrovascular disease (CVD) and had had an infarct or haemorrhage involving the dentate-olivary tract (Table 1). They comprised two women and 14 men who had been bedridden and had survived for periods ranging from 2 days to 142 months after the onset of CVD. Their ages at the time of death were 57–82 years (mean 67.3 years).

To estimate accurately the changes involved in IOH after the onset of CVD, patients in whom the time of onset of the primary lesion responsible for IOH was uncertain and who did not have a detailed medical record regarding the time course of SPT were excluded from this analysis. Three patients with unilateral IOH were also excluded since there is no definite correlation between the process of IOH and the generation and persistence of SPT. Six patients without CNS lesions were examined as age-matched controls.

Clinical investigation
All of the following issues were investigated for every subject from the clinical descriptions in the medical records: (i) the presence or absence of SPT; (ii) the interval from the onset of CVD to the appearance of SPT; (iii) the time course of the change in the distribution and intensity of SPT; and (iv) the presence or absence of other visible tremorous movements synchronized with SPT, if they existed. Five neurologists, who were well acquainted with involuntary movements, evaluated the magnitude and distribution of SPT during life by visual diagnosis at least once a month. Electrophysiological techniques were not used in this study.

Histopathology
Brain tissue was fixed for ~3 weeks in 4% formaldehyde buffered with 0.1 M phosphate (pH 7.4). Most of the tissue blocks were embedded in paraffin after dehydration through a
graded series of ethanol solutions. The brainstem was cut into 3 \( \mu \)m serial sections and the cerebellum was cut sagittally into 6 \( \mu \)m serial sections. Thin sections were stained both conventionally, with haematoxylin, eosin and luxol fast blue (H&E + LFB), and immunohistochemically, with antibodies against synaptophysin (SY-38; monoclonal antibody, 1 : 200; Chemical Credential, Aurora, Ohio, USA) as a marker of presynaptic vesicles, against neurofilaments [to neurofilament 1 (NF-1); monoclonal antibody, 1 : 200; Medac, Copenhagen, Denmark] and against glial fibrillary acidic protein (GFAP; polyclonal antibody, 1 : 4800; Dako, Hamburg, Germany) as an astrocyte marker. The immunohistochemistry was carried out using an avidin–biotin–peroxidase complex method (Hsu et al., 1981).

To measure the area of the inferior olivary nuclei (ION) and to count the number of olivary neurones, we used H&E + LFB-stained sections in which the bilateral olivary nuclei were symmetrically and clearly located. Each olivary nucleus was divided into the following elements using photographs of sections at \( \times 143 \) magnification: the amiculum (composed of afferent fibres), hilus (composed of efferent fibres) and ribbon (composed of neurones, neuropil and glial cells). We traced the borders and measured the total areas of each olive using a digital analysis system (Quantimet Q 500; Leica, UK). The dorsal and ventral poles of the ribbon were connected by a straight line, which was regarded as the medial border of the olive (line A in Fig. 1). At this part of the hilus, we counted (NF-1)-immunopositive axons at \( \times 400 \) magnification for the quantitative evaluation of the efferent fibres from the olive. The number of axons was determined from the distance between the ventral and dorsal poles at the hilus (line A in Fig. 1).

When counting the neurones in the ribbon, we distinguished hypertrophic neurones from neurones with normal appearance by their shape and size at \( \times 200 \) magnification.

### Results

Out of 16 cases, nine showed an infarct and seven a haemorrhage. Ten cases showed macroscopic bilateral hypertrophic changes of the ION. In the remaining six patients, who had died \( \leq 21 \) days after CVD onset, the ION was macroscopically normal in shape and size (Table 1).

#### Clinical time course of SPT

SPT appeared in eight patients (Table 2). It took at least 1 month for SPT to develop after the primary lesion occurred in the dentate-cerebellar tract. In seven patients, SPT appeared 1–2 months after lesions developed in the dentate-olivary tract. SPT became increasingly intense and more widely distributed in all the patients, reaching a peak between 5 and 24 months. From the peak of SPT, its magnitude and the muscles involved persisted until death.

### Table 2 Clinical course and neurological findings in patients presenting with SPT

<table>
<thead>
<tr>
<th>Patient</th>
<th>Emergence of SPT</th>
<th>Peak of SPT</th>
<th>Dominant site of SPT</th>
<th>Eyeball</th>
<th>Face</th>
<th>Diaphragm</th>
<th>Extremities</th>
</tr>
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<tbody>
<tr>
<td>13</td>
<td>1 month</td>
<td>8 months</td>
<td>Bilateral</td>
<td>–</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>8</td>
<td>1 month</td>
<td>5 months</td>
<td>Left &gt; right</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>14</td>
<td>1 month</td>
<td>22 months</td>
<td>Left &gt; right</td>
<td>–</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>11</td>
<td>1 month</td>
<td>15 months</td>
<td>Bilateral</td>
<td>+</td>
<td>++</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>10</td>
<td>1 month 15 days</td>
<td>9 months</td>
<td>Left &gt; right</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>–</td>
</tr>
<tr>
<td>16</td>
<td>1 month 21 days</td>
<td>24 months</td>
<td>Right &gt; left</td>
<td>++</td>
<td>+</td>
<td>–</td>
<td>++</td>
</tr>
<tr>
<td>9</td>
<td>2 months 12 days</td>
<td>6 months</td>
<td>Right &gt; left</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>15</td>
<td>4 months</td>
<td>17 months</td>
<td>Bilateral</td>
<td>–</td>
<td>++</td>
<td>++</td>
<td>–</td>
</tr>
</tbody>
</table>

Neurological findings (evaluated visually): – = no tremor; + = mild to moderate; ++ = severe.
Histopathological findings

Time course

Initial enlargement of neurones, with swelling of the cytoplasm and formation of vacuoles, was observed 21 days after CVD onset; these changes reached a peak ~6–7 months after onset. The hypertrophic changes of neurones decreased over 2 years in association with a reduction in the total number of neurones.

Demyelinative change revealed by LFB staining, was detected in the ribbon at 21 days, in the amiculum at 40 days and in the hilus at 6 months after onset. Myelin almost completely disappeared from the ribbon after 7 months and from the amiculum and hilus after 29 months (Fig. 2).

The number of neurofilament-immunopositive axons began to decrease in the ribbon 21 days after disease onset and in the amiculum and hilus at 40 days, though numerous positive axons were present in controls. During the later stages, axonal degeneration, characterized by fragmentation, advanced gradually. In subjects who had survived for 6 months, axonal terminals were often enlarged and club-shaped, and axons accumulated around the neurones or formed tangles in the neuropil at a distance from the neuronal soma (Fig. 3).

Using the anti-synaptophysin antibody, which recognizes synaptic vesicle proteins in presynaptic terminals, a diffuse distribution of synaptic vesicles was observed in the ribbons of the controls. Synaptic vesicles were only sparsely stained from 40 days after onset. Although positive synaptic vesicles were rare after 6 months, there were focal clusters of immunoreactive dots around the residual neurones. Some of the stained vesicles invaginated into the neuronal cytoplasm. These findings were also detected in the subject who had survived for 142 months after CVD onset.

Immunostaining for GFAP showed that astrocytes in the control subjects and in subjects who had died shortly after disease onset (within 10 days) had a small amount of cytoplasm and a few delicate processes. Many astrocytes showed an increase in the expression of GFAP and had protoplasmic cytoplasm 21 days after onset. Six months after onset, numerous astrocytes had intense GFAP staining, enlarged gemistocytic cytoplasm and many well-developed cell processes. The fibrillary astrocytes were more abundant than the gemistocytic variety in the cases surviving >2 years. However, even in cases surviving >6 years there were a few gemistocytic astrocytes coexisting with fibrillary ones.
Fig. 3 Histopathological alteration in inferior olivary hypertrophy. (A, E, I and M) A case 10 days after stroke onset, showing neurones (A), axons (E), synaptic terminals (I) and astrocytes (M) with almost normal appearance. (B, F, J and N) A case of IOH 40 days after onset, showing neuronal ballooning (B), slightly decreased immunoreactivity of axons (F) and synaptic terminals (J), and definite protoplasmic astrocytes (N) in the ribbon. (C, G, K and O) A case 6 months after onset, showing ballooned neurones with vacuoles as well as gemistocytic astrocytes (C, O), some anti-neurofilament antibody-positive plump neurones and swollen axons with strong immunoreactivity (G), and decreased anti-synaptophysin antibody-positive granules of axon terminals with a tendency to focal accumulation (K). (D, H, L and P) A case 88 months after onset, showing a normal-shaped neurone in the neuropil, which was diffusely occupied by fibrillary astrocytes whose staining for GFAP had become sparse (D, P), clustering of axonal terminals distant from residual neurones (H), and synaptic terminals distributed around the soma of a residual neurone despite loss of those in the neuropil. A–D, H&E + LFB staining; E–H, anti-NF-1 immunostaining; I–L, anti-SY-38 immunostaining; M–P, anti-GFAP immunostaining. Magnification ×320.
Area of the ION and number of olivary neurones

The total area of the principal olivary nuclei in the control subjects (mean ± SD) was 10.92 ± 0.81 mm². In the 16 cases, IOH was recognized macroscopically in those who had survived >40 days after disease onset, whereas neuronal hypertrophy was first observed microscopically 21 days after onset. The total area of the nucleus increased gradually to reach an area nearly twice as large as that in the controls (~16 months after disease onset). The total area started to decrease below that in the controls 6 years after disease onset (Figs 4 and 5, Table 3).

The total number of neurones in the ribbon (mean ± SD; values for the right and left sides were averaged) was 879.8 ± 66.3 in the control subjects. In the 16 cases, the total number of neurones was almost the same or slightly less than that in the control subjects 6 months after onset. The number then began to decrease linearly and was only ~10% of that in the control subjects (almost ≤ 100) 6 years after onset.
Enlarged neurones were observed in the ribbon 21 days after onset; their number increased gradually for up to 6 months and then decreased, with a time course similar to that of the total number of neurones. Thus, neuronal loss became evident just after the number of enlarged neurones had peaked. However, even in the subjects with long survival (>6 years), there were dozens of neurones with an almost normal appearance mixed with enlarged or atrophic neurones. There were 81 neurones out of a total of 94 that appeared normal in the subject who survived 88 months and 52 out of 64 in the subject surviving 142 months.

Number of neurofilament-immunopositive axons at the hilus
The number of efferent fibres from the olive at the hilus (mean ± SD) was 30.4 ± 2.7/100 μm in six normal controls. The number of efferents decreased in patients surviving >6 months, and finally to <10 fibres/100 μm (Figs 1 and 6, Table 3). In addition to the decrease in the number of efferents, a difference in the morphological characteristics of the axons was observed. In normal controls, fine fibres with slight NF-1 immunoreactivity ran parallel with each other towards the contralateral inferior cerebellar peduncle (Fig. 6A). On the other hand, almost all efferent fibres were swollen and kinky and had relatively strong NF-1-immunoreactivity in a patient who survived >6 years (Fig. 6B).

Discussion
This study showed that SPT appeared just after olivary neurones initially became hypertrophic, and it peaked in intensity and distribution just after the peak of hypertrophic change in the olivary neurones in most cases. From these findings, we consider that IOH was attributable directly to the generation of SPT. However, SPT did not subside at all for >6 years after its onset in three subjects who showed marked neuronal loss and breakdown of their efferent fibres in the atrophic inferior olives.

The mechanism underlying the unique hypertrophic change of the olive remains unclear. The inputs from the dentate nucleus to the olive, passing through the central tegmental tract, are almost entirely GABAergic inhibitory fibres (Sotelo et al., 1986), in contrast to the other inputs, such as the those in the spino-olivary tract and the mesodiencephalon olivary tract, which are substantially glutaminergic excitatory fibres (De Zeeuw et al., 1998). These afferents connect to the olivary gap junctions, which are dendro-dendritic synapses, and inhibit neuronal activity coupling, giving rise to autonomous firing in the olive (Llinás and Yarom, 1986; Manor et al., 1997). Therefore, an excess of excitatory inputs would be one of the important factors that relate to the enlargement of neurones and astrocytes in early IOH and the subsequent neuronal loss and sustained astrocytosis in the late stage.

Electron microscopic findings showed that, in neurones during early IOH, numerous round, electron-dense granules, indicating ribosomes, were detected within expanded cisternal profiles of the rough endoplasmic reticulum in a subject who survived for only 6 days after interruption of the dentate-olivary tract (Barron et al., 1982; Yagishita et al., 1986). A histochemical study demonstrated failure in the transport of acetylcholinesterase from the neuronal soma to neuropil through the dendrites (Koeppe et al., 1980). These findings suggest that the synthesis and transport of proteins or proteinaceous enzymes begin to be disturbed in hypertrophic neurones in the olive even during the early stages of IOH (Kreutzberg et al., 1975). Our findings indicate that marked

<table>
<thead>
<tr>
<th>Patient</th>
<th>Time After stroke</th>
<th>Total area of olivary nucleus (mm²)</th>
<th>Area of ribbon (mm²)</th>
<th>Total number of neurones³</th>
<th>Number of hypertrophic neurones³</th>
<th>Number of efferent fibres from olive⁸</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 days</td>
<td>11.08</td>
<td>3.62</td>
<td>862</td>
<td>0</td>
<td>28.8</td>
</tr>
<tr>
<td>2*</td>
<td>5 days</td>
<td>11.66</td>
<td>6.49</td>
<td>927.5</td>
<td>0</td>
<td>28.1</td>
</tr>
<tr>
<td>3</td>
<td>5 days</td>
<td>9.12</td>
<td>4.11</td>
<td>748</td>
<td>0</td>
<td>36.7</td>
</tr>
<tr>
<td>4*</td>
<td>8 days</td>
<td>9.43</td>
<td>4.32</td>
<td>845</td>
<td>0</td>
<td>32.5</td>
</tr>
<tr>
<td>5</td>
<td>10 days</td>
<td>8.21</td>
<td>4.29</td>
<td>831.5</td>
<td>0</td>
<td>37.5</td>
</tr>
<tr>
<td>6</td>
<td>21 days</td>
<td>9.28</td>
<td>4.01</td>
<td>681</td>
<td>14.5</td>
<td>27.1</td>
</tr>
<tr>
<td>7</td>
<td>40 days</td>
<td>12.77</td>
<td>6.64</td>
<td>817</td>
<td>89.5</td>
<td>26.1</td>
</tr>
<tr>
<td>8*</td>
<td>6 months 8 days</td>
<td>15.21</td>
<td>8.32</td>
<td>688.5</td>
<td>362</td>
<td>16.6</td>
</tr>
<tr>
<td>9##</td>
<td>7 months 15 days</td>
<td>17.82</td>
<td>9.23</td>
<td>653</td>
<td>262</td>
<td>15.6</td>
</tr>
<tr>
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<td>15 months</td>
<td>17.06</td>
<td>8.7</td>
<td>450</td>
<td>168</td>
<td>8.0</td>
</tr>
<tr>
<td>11##</td>
<td>16 months</td>
<td>19.4</td>
<td>7.45</td>
<td>606.5</td>
<td>202.5</td>
<td>11.7</td>
</tr>
<tr>
<td>12*</td>
<td>17 months</td>
<td>15.67</td>
<td>7.75</td>
<td>466.5</td>
<td>130.5</td>
<td>13.2</td>
</tr>
<tr>
<td>13†</td>
<td>29 months</td>
<td>12.2</td>
<td>6.35</td>
<td>262</td>
<td>37</td>
<td>9.7</td>
</tr>
<tr>
<td>14†</td>
<td>80 months</td>
<td>6.19</td>
<td>2.39</td>
<td>100</td>
<td>15.5</td>
<td>9.1</td>
</tr>
<tr>
<td>15†</td>
<td>88 months</td>
<td>6.2</td>
<td>2.91</td>
<td>93.5</td>
<td>12.5</td>
<td>11.6</td>
</tr>
<tr>
<td>16†</td>
<td>142 months</td>
<td>9.62</td>
<td>3.69</td>
<td>63.5</td>
<td>11</td>
<td>8.0</td>
</tr>
</tbody>
</table>

Patients: *with haemorrhage; unmarked = infarct; #developed SPT. ³Average for right and left nuclei in subjects with normal-shaped and bilaterally hypertrophic ION; ⁴number of immunopositive axons per 100 μm for neurofilaments at the hilus.
neuronal loss started after the peak of neuronal hypertrophy; this also supports the hypothesis that the hypertrophic change of olivary neurones marks the presence of a dysfunctional process leading to neuronal death after hyperexcitation. Our findings also indicate that the inferior olive or dentato-olivary pathways might function as an inhibitor for the generation of SPT. That is, SPT might represent the release of the primitive rhythmicity that exists in the brainstem and is suppressed in the normal condition (Yakovlev, 1956; Kane and Thach, 1989).

Lapresle and Hamida reported that the delay between interruption of the dentate-olivary tract and the appearance of SPT is usually a few weeks but may range from 1 day to 30 months (Lapresle and Hamida, 1970). Matsuo and Ajax reported that it ranges from 2 to 49 months with a median between 10 and 11 months (Matsuo and Ajax, 1979), although they include cases in which the time of onset of primary lesions is not known for certain. In our study, the median duration of the delay in the eight SPT patients was between 1 and 2 months from the causative lesions, which is within the range of the averages reported in previous studies.

Regarding extraneuronal components of the IOH, prominent astrocytosis had contributed primarily to longstanding IOH after the stage of marked neuronal loss for >1 year after the onset of causative lesions. As gemistocytic astrocytes were replaced by fibrillary ones, the whole olive decreased in size and finally became atrophic >6 years later. The unusual synaptic cluster, detected after 6 months from the onset of the causative lesions, was probably due to remodelling through the development of collateral sprouts corresponding to the interruption from the major afferent fibres. As regards synaptic alteration, Kawanami and colleagues reported that synaptic vesicles were irregularly clustered around and inside the neuronal soma in four patients with IOH, despite decreased activity in the neuropil, where products reactive with synaptophysin were found diffusely in the normal controls (Kawanami et al., 1994). The input from other afferent fibres to the inferior olive (Brodal et al., 1950; Brown, 1974) could contribute to the long processes during which residual neurones and active astrocytosis coexist for >10 years and to the gradual remodelling of synaptic and axonal terminal processes.

To date, most authors have attributed the generation of SPT to the abnormal function of the inferior olives because of both the characteristic hypertrophic changes and the rhythmicity of the olivary neurones, which corresponds to the 2–3 Hz frequency of SPT. Llinás has suggested that SPT may be based on hypersynchronous firing of olivary neurones that have the intrinsic property of an oscillator (Llinás, 1984). Interruption of the dentate-olivary tract, which consists of GABAergic inhibitory fibres to the gap junctions of olivary neurones, has been thought to lead to hypersynchronous discharge. Although this hypothesis has been accepted widely, data indicating that the hyperactivity of neurones in IOH causes SPT have not been available. Dubinski and colleagues showed that, clinically, there was increased glucose metabolism throughout the medulla of patients with SPT, and this led to the hypothesis that hyperactivity of the inferior olive may bring about the IOH and produce SPT (Dubinsky et al., 1991). However, the ability to distinguish between the inferior olive and other structures in the medulla, such as the nucleus ambiguus, is beyond the current limit of resolution of PET.

Although early IOH, probably caused by the excess of excitatory input, might trigger the development of SPT, the persistence of the abnormal rhythm (once established) for more than several years cannot be due to residual neurones in the atrophic olives. Because a few inferior olivary neurones could generate a discharge similar to that produced by the whole nucleus through electrical coupling via dendrodendritic gap junctions (Manor et al., 1997), it is theoretically possible that <100 neurones generate SPT in subjects who survive for several years. However, the following two findings are incompatible with such hypotheses. First, both the myelin and axons of efferent fibres from the olive had

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**Fig. 6** Efferent fibres (olivocerebellar projections) at the olivary hilus (line A in Fig. 1). Anti-NF-1 immunostaining; magnification ×50. (A) Normal controls, showing fine dense efferents, slightly immunoreactive for NF-1, running in the same direction. (B) A patient who survived for 142 months, showing only a few swollen, kinky fibres without a regular course in the hilus.
degenerated almost completely; secondly, SPT persisted for the rest of the subject’s life without any decrement in its intensity and distribution.

SPT has been considered to be a prototype of involuntary hyperkinesic movement produced by a central pacemaker (Vidailhet et al., 1998). Kane and Thach speculate that the physiological basis of SPT is hyperactivity not of the olive but of the nucleus ambiguus and the dorsolateral reticular formation adjacent to it (Kane and Thach, 1989). Although it has not yet been proven that the neurones in the nucleus ambiguus, unlike those of the inferior olive, can fire autonomously (Mendelowitz, 1996), this theory is compatible with our conclusion that SPT persisted over several years and did not depend on altered activity caused by atrophic changes of the olivary nucleus. However, as the nucleus ambiguus projects ipsilaterally, and not contra- or bilaterally, this hypothesis is contrary to the present view which is widely accepted, that unilateral IOH always leads to contralateral SPT in living patients (Deuschl et al., 1990, 1994).

We consider that there are two underlying mechanisms that might evoke SPT. One possibility is that undetected generators somewhere in the brainstem become the source of SPT when they are released from inhibitory inputs from the olive; the activity of these generators would be suppressed by the inferior olives in the normal condition. The other possibility is that the development of SPT and its persistence after its peak is due to hyperactivity of olivary neurones that are in a state of denervated hypersensitivity from 1–2 months after onset, because of the blockade of inhibitory inputs over several years.

Regardless of whether or not the underlying mechanism that generates SPT is based on early IOH, we conclude from the clinicopathological correlation that the persistence of peak intensity and the distribution of once-established SPT are probably due to the disturbance of neuronal networks that maintain natural rhythmicity in the body, resulting from the dysfunction of the olive. The inferior olive has a significant role in the transmission of signals to the cerebellum in order to produce skilled movement and motor learning (Llinas et al., 1975; Darlot, 1993). Thus, in addition to the possible existence of other generators of SPT, the lack of feedback from abnormal movement may contribute to the considerable persistence of SPT in subjects surviving ≥1 year, in whom the inferior olives has become dysfunctional (Hefter et al., 1992).

This study was based on a retrospective analysis of patient data, and as such has two limitations. One is the lack of quantitative analysis of the chronological evaluation of SPT in each patient, and another is that the morphometric analysis of various components of the olive—a three-dimensional nucleus—was done on one two-dimensional sample. In spite of these limitations, we believe that our data provide evidence suggesting a lack of correlation between the persistence of established SPT and the slow degenerative process of IOH.

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