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The distribution and dynamic density of oligodendroglial cytoplasmic inclusions (GCIs) in multiple system atrophy: a correlation between the density of GCIs and the degree of involvement of striatonigral and olivopontocerebellar systems

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Abstract The distribution and dynamic density of oligodendroglial cytoplasmic inclusions (GCIs) were studied based on 30 cases of multiple system atrophy (MSA), including striatonigral degeneration (SND), olivopontocerebellar atrophy (OPCA) and Shy-Drager syndrome. GCIs were widely spread throughout the central nervous system, including the striatonigral and olivopontocerebellar systems. Inclusion-bearing cells appeared to be oligodendrocytes which usually had larger and lighter nuclei than those of normal-looking oligodendrocytes. The distribution of GCIs was similar in all cases, irrespective of the degrees of OPCA and SND, but the frequency of GCIs varied from case to case. We classified all the cases into two categories based on the degree of neuropathological changes of SND (mild and severe) and, independently, into three groups based on that of OPCA (minimal, moderate, and severe), i.e., a total of six groups. An association between the frequency of GCIs and the severity of the lesions was obtained. For example, many GCIs exist in the cerebellar white matter in the cases in which OPCA was not histologically confirmed. More GCIs were seen in the cases with moderate OPCA. In the cases with severe OPCA, GCIs were rarer and smaller, in proportion to the devastation of fibers; no GCIs were seen in the cases with more severe OPCA. The incidence of GCIs showed a positive correlation to the severity of OPCA but not that of SND in the corticopontine tracts, of both OPCA and SND in the pyramidal tracts, and of SND but not of OPCA in the pencil fibers of the putamen. It is suggested that GCIs may represent either a change synchronous with neuronal degeneration or a phenomenon preceding neuronal changes, especially in the cerebellar white matter. Thus, they may represent the early changes in MSA and may be a useful neuropathological hallmark for diagnosis of MSA, even in cases with minimal OPCA and SND.

Key words Multiple system atrophy · Oligodendroglial cytoplasmic inclusion · Distribution · Evolution

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Introduction

The concept of multiple system atrophy (MSA) was established between 1969 and 1984 by Oppenheimer and colleagues [11, 20, 21] to be a clinicopathological unity of sporadic olivopontocerebellar atrophy (OPCA) [9], striatonigral degeneration (SND) [3] and Shy-Drager syndrome [25]. The degeneration of the affected neurons has been studied [26, 28] and, recently, glial cell changes, especially the oligodendroglial cytoplasmic inclusions (GCIs) in MSA (best detected by Gallyas-Braak silver development), and their distribution in the central nervous system have been reported to be essentially similar [1, 2, 4–8, 10, 12–19, 22–24]. However, the incidence of GCIs varied from report to report, and from case to case. The incidence of GCIs has been assumed to increase in proportion to the degrees of OPCA or SND [10, 14, 16, 18, 19, 23, 24]; however, for example, the cerebellar white matter, which is one of the predilection sites of GCIs [18, 19, 23, 24], has only few GCIs in the cases with severe OPCA [1, 2, 4, 16]. Thus, the association of the severity of degenerative lesions to the density of GCIs is not clear. During a systematic investigation of 30 MSA cases, we have found that the individual incidence of GCIs depends on the degrees of OPCA and SND, and we document the dynamic processes of GCIs and their significance for a diagnosis of MSA in the early stage.

Table 1 Summary of cases studied. The 30 MSA cases are grouped into six categories according to the degrees of severity of OPCA or SND: – none, ± minimal, + mild, ++ moderate, +++ severe (*MSA* multiple system atrophy, *OPCA* olivopontocerebellar atrophy, *SND* striatonigral degeneration, *SG* sponge-like gliosis in the cerebellar white matter)

Case	Age	Sex	OPCA	SG	SND	Case	Age	Sex	OPCA	SG	SND
Group 1: OPCA (–) SND (–)						*Group 5: OPCA (+) SND (+)*					
1	72	M	±	–	±	15	56	F	++	±	++
2	48	M	±	–	±	16	63	F	++	–	++
3	47	M	±	–	±	17	62	M	+++	–	+
Group 2: OPCA (+) SND (–)						18	59	M	+++	–	++
4	65	F	+++	–	±	*Group 6: OPCA (++) SND (+)*					
5	71	M	+++	–	±	19	53	M	+++	+	+
6	50	M	+++	–	±	20	62	F	+++	+	+
7	71	M	+++	–	±	21	59	M	+++	+	+
Group 3: OPCA (++) SND (–)						22	62	M	+++	+	++
8	52	M	+++	+	±	23	59	F	+++	+	++
9	72	M	+++	+	±	24	50	F	+++	+	++
10	60	M	+++	+	±	25	50	M	+++	+	++
11	66	F	+++	+	±	26	60	M	+++	+	++
Group 4: OPCA (–) SND (+)						27	61	F	+++	+	++
12	65	M	±	–	++	28	71	F	+++	+	++
13	76	M	+	–	++	29	70	M	+++	+	++
14	56	M	+	–	++	30	56	F	+++	+	++

Subjects and methods

The brains and spinal cords from 30 patients suffering from MSA with various combinations of SND, OPCA and autonomic failure were used in this study (Table 1). The cases were neuropathologically diagnosed as having MSA [21, 26].

For light microscopy, the brains were fixed in 10% formalin for 1–3 weeks, after which the whole brain was cut into 1-cm-thick coronal slices. Five large coronal hemispheric slices taken at different levels, transverse slices of the mesencephalon, pons and medulla oblongata and several segments of the spinal cord were embedded in paraffin wax. In addition to the routine histological stains such as hematoxylin-eosin (H&E), Klüver-Barrera, Holzer and Bodian's silver impregnation, Gallyas-Braak silver development, which is the most sensitive for demonstrating GCIs, was applied for counting GCIs.

A semiquantitative evaluation of GCIs was performed manually using a × 40 objective, and the count was taken as an average number of GCIs in five fields. All cases were divided into groups based solely on the histopathological findings, such as neuronal loss and gliosis, in the striatum and substantia nigra (SND), and in the pontine nuclei, cerebellum and inferior olivary nucleus (OPCA). We classified the 30 MSA cases into two groups by the degree of SND, i.e., minimal to mild, and moderate to severe; and, independently, into three groups by the severity of OPCA, i.e., minimal, mild to moderate, and severe (a total of six groups; Table 1).

Results

Morphology of GCIs

Numerous GCIs were seen in all cases examined. GCIs varied in stainability, from pale to bright pink, with H&E stain. They were also stained with Bodian's silver impregnation but were best detected by the Gallyas-Braak method. The nuclei of the GCI-bearing cells usually seemed to be slightly bigger than those of normal-looking oligodendrocytes. GCIs were cone- or flame-like in shape on Gallyas-Braak preparations, the size of which varied from inclusion to inclusion. GCIs were also seen in interfascicular oligodendrocytes and often appeared in rows between myelinated fibers. GCIs were clearly distinct from the coiled or thread-like profiles of glial argyrophilic inclusions seen in progressive supranuclear palsy [30] and in corticobasal degeneration [27].

Distribution of GCIs

The distribution of the GCIs showed a characteristic pattern, which was essentially similar in all cases, irrespective of the severity of OPCA or SND, and was in accordance with many previous reports [8, 18, 19, 22–24]. GCIs were more frequent in the white matter than the gray matter, being prominent in the pencil fibers of the putamen, the internal capsule, external capsule, corpus callosum, anterior commissure, corticopontine tract, pyramidal tract, cerebellar white matter, and the subcortical white matter of the parietal lobe (primary motor and premotor areas) and frontal lobe (supplementary motor cortical area). GCIs also existed in the gray matter, such as the putamen (especially dorsolateral part), caudate nucleus, globus pallidus nucleus and inferior olivary nuclei. Very few GCIs were seen in the subthalamic nuclei, superior cerebellar peduncle, cerebellar cortex, the hilus of the dentate nucleus and the dorsal column of the spinal cord.

Incidence of GCIs

Even in the same region, the incidence of GCIs varied from group to group. In the cerebellar white matter, the number of GCIs was 10–20/high-power field (HPF) in groups 1 and 4 (with minimal OPCA, Fig. 1a–d), more than 20/HPF in groups 2 and 5 (with mild to moderate

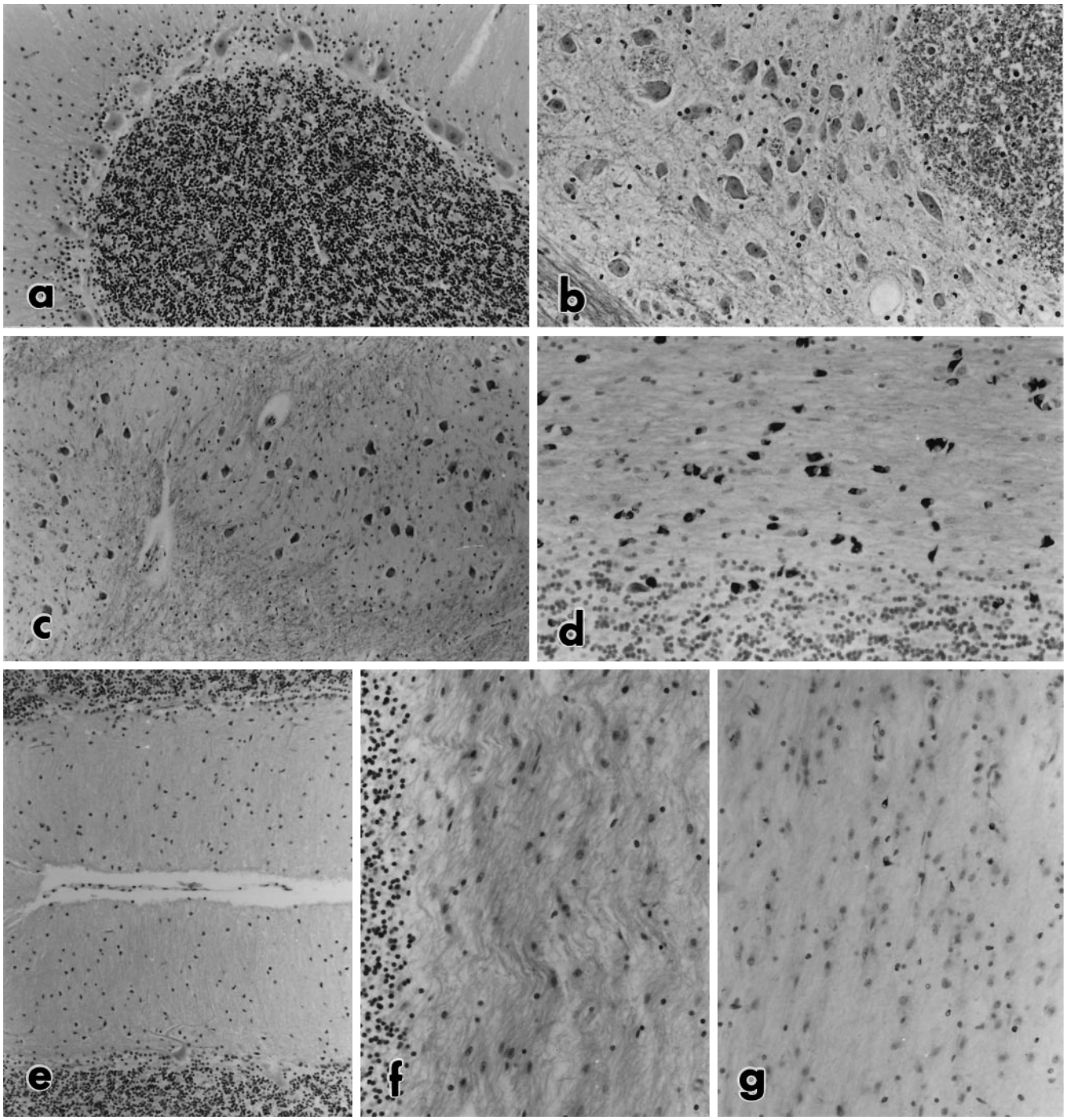

Fig. 1 a–d An MSA case with minimal OPCA (case 1). Purkinje cell layer (**a**, H&E), inferior olivary nucleus (**b**, Klüver-Barrera) and pontine nucleus (**c**, Klüver-Barrera) are all well preserved. Histopathologically, OPCA is not apparent. The cerebellar white matter has many GCIs (**d**, Gallyas-Braak). **e–g** An MSA case with severe OPCA (case 10). Most Purkinje cells are lost (**e**, H&E). The cerebellar white matter shows devastation of myelinated fibers and severe astrocytic glial fibrosis (**f**, Holzer). Only few GCIs are seen. The size of GCIs is smaller (**g**, Gallyas-Braak) than that in case 1. (*MSA* multiple system atrophy, *OPCA* olivopontocerebellar atrophy, *H&E* hematoxylin-eosin, *GCIs* oligodendroglial cytoplasmic inclusions). **a, e** × 50; **b–d, f, g** × 100

OPCA), but only 1–5/HPF in groups 3 and 6 (with severe OPCA, Fig. 1e–g). GCIs were rarely observed in the cases with severe devastation of the cerebellum. The incidence of GCIs in the cerebellar white matter depended only on the severity of OPCA and not on that of SND.

In the corticopontine tracts, both the frontopontine and parieto-temporo-occipitopontine tracts, the number of GCIs was 5–10 in groups 1 and 4 (with minimal OPCA, Fig. 2a, b), 10–20 in groups 2 and 5 (with moderate OPCA), and more than 20 in groups 3 and 6 (with severe OPCA, Fig. 2c, d). The incidence of GCIs in these tracts depended only on the severity of OPCA, and not that of SND (Fig. 2a–d).

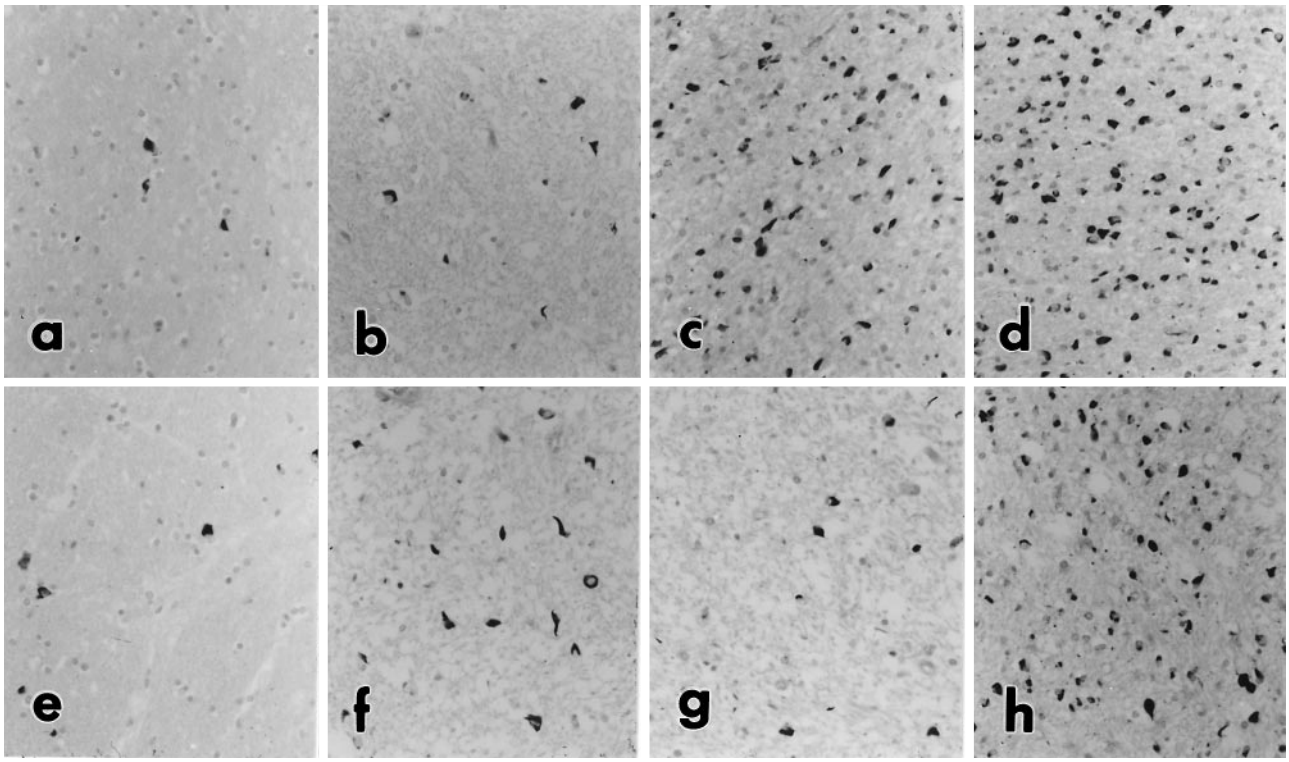

Fig. 2 GCIs in the corticopontine tract (**a–d**) and the pyramidal tract (**e–h**) in the mesencephalon. **a**, **e** Case 1 with minimal OPCA and SND. **b**, **f** Case 14 with minimal OPCA and severe SND. **c, g** Case 10 with severe OPCA and mild SND. **d**, **h** Case 22 with severe OPCA and SND. (*SND* Striatonigral degeneration). **a–h** Gallyas-Braak stain, × 400

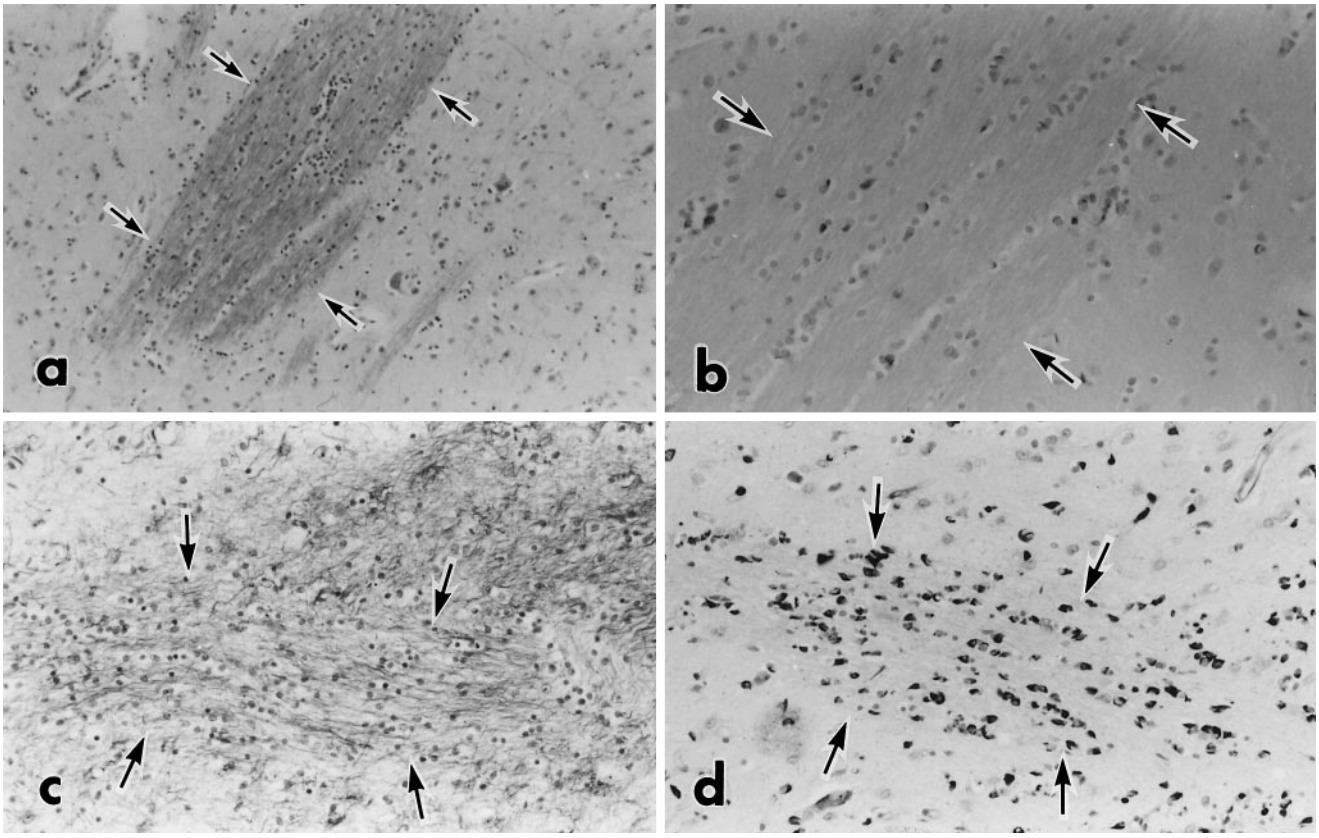

Fig. 3 a–d Pencil fibers in the putamen. **a** Case 1 with minimal OPCA and SND. The neurons of the putamen are spared. Oligodendroglial cells in the bundle are also well preserved (Klüver-Barrera). **b** Adjacent section to that shown in **a**. A few GCIs are seen (Gallyas-Braak). **c** Case 14 with minimal OPCA and severe SND. Severe fibrillary gliosis is seen in the pencil fibers (Holzer). **d** Adjacent section to that shown in **c**. Numerous GCIs are seen in the pencil fibers. The size of GCIs are larger than in case 1. *Arrows* show the pencil fibers (Gallyas-Braak). **a** × 90, **b–d** × 180

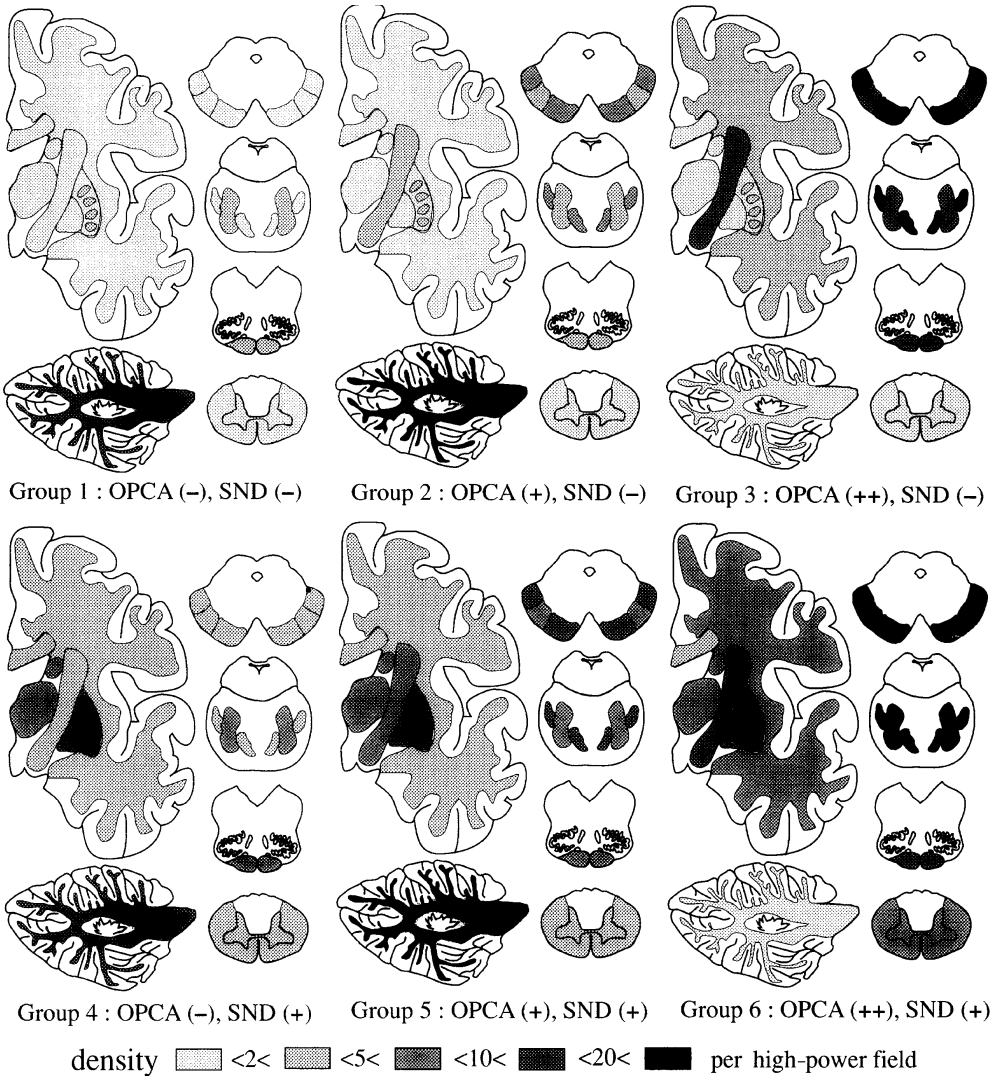

Fig. 4 Mapping of distribution and dynamic process of GCIs in representative sections of central nervous system

In these tracts, myelinated fibers seemed well preserved even in severe OPCA cases, and no devastation of the tracts was seen. No difference in size of GCIs was seen among the six groups (Fig. 2a–d).

In the pyramidal tract, the number of GCIs was 1–5 in group 1 (with minimal OPCA and SND, Fig. 2e), 5–10 in group 4 (with severe SND and minimal OPCA, Fig. 2f) and group 3 (with severe OPCA and mild SND, Fig. 2g), and 10–20 in group 6 (with severe OPCA and SND, Fig. 2h). Again no difference in the size of GCIs was seen between the six groups (Fig. 2e–h).

The frequency of GCIs in the internal capsule was similar to that in the pyramidal tract. GCIs in the cerebral white matter, corpus callosum and anterior commissure were rarer than in the pyramidal tract and internal capsule (less than 10), although they showed the same correlation with the severity of OPCA and SND as that for the pyramidal tract.

In the pencil fibers of the putamen, the number of GCIs was 5–10 in groups 1–3 (with mild SND, Fig. 3a, b), and more than 20 in group 4–6 (with severe SND, Fig. 3c, d). Their incidence was closely correlated to the severity of SND and not to that of OPCA. Even in the cases with severe degeneration of the putamen which showed a sponge-like appearance, the pencil fibers were relatively spared; the number of oligodendrocytes was also spared.

In gray matter, e.g., the pontine nucleus, putamen, caudate nucleus and inferior olivary nucleus where many GCIs were observed, the association of GCIs to the degree of OPCA or SND was equivocal. The distribution and dynamic processes of GCIs in the central nervous system are illustrated in Fig. 4.

Discussion

GCIs were widely distributed throughout the central nervous system of all the MSA cases examined. The predilection sites of GCIs were not only in the regions known to be frequently affected in OPCA and SND, but also in areas such as the cerebral white matter, pyramidal tracts, internal capsule and spinal cord. The optic nerve, optic tract and dorsal column of the spinal cord were free of GCIs. In the cerebral white matter, GCIs were most abun-

dant in the subcortical areas of the motor cortex, the premotor cortex and the supplementary motor cortex. More GCIs were found in the frontoparietal than in the temporal and occipital white matter. This characteristic topography of GCIs in MSA was similar in all cases, and was mostly compatible with previous reports [8, 18, 19, 22–24]. However, the incidence of GCIs varies considerably among these reports, even when the differences in the sensitivity of Gallyas stain or thickness of the sections are taken into consideration.

The incidence of GCIs has previously been assumed to increase in proportion to the degrees of histopathological changes [10, 14, 16, 18, 19, 23, 24]. Papp et al. [23] mentioned the relationship between the density of GCIs in some areas of gray matter and the severity of their neuronal alternation; however, they only focused on gray matter and not white matter. Mochizuki et al. [16] examined six and Costa et al. [8] nine MSA cases with different degrees of OPCA and SND. They presented the incidence of GCIs, but no details of the dynamic process of GCIs. The incidence of GCIs has also been described [10, 14, 18, 22], but their association to the severity of lesions was not mentioned. Thus, no systematic examination of the incidence and dynamic processes of GCIs has been performed as far as we know. We believe that this is the first report on the dynamic development of GCIs in association with the severity of the lesions. In this study, we assigned 30 MSA cases to six groups according to the severity of OPCA and SND and found a correlation between the incidence of GCIs and the severity of OPCA and SND, although we cannot offer any evidence that OPCA or SND progresses along a stereotypic chronology.

In the cerebellar white matter, where a common lesion is seen in cases of MSA and which has been reported to be a predilection site for GCIs [8, 18, 19, 23, 24], GCIs have been reported to be frequent [4, 16, 18, 19, 23, 24], or rare [1, 2, 4, 14, 16]. Cases with severe OPCA were not always shown to have many GCIs. In this study, a large number of GCIs were detected even in the cases in which OPCA was not histologically apparent. In the cases with moderate OPCA, the number of GCIs was increased to some extent. In the cases with severe OPCA, GCIs decreased in number in proportion to the devastation of nerve fibers. Finally, most GCIs had disappeared in cases with more severe OPCA.

The densities of GCIs in the cerebellar white matter have been rarely mentioned in previous reports. Mochizuki et al. [16] reported that a case of MSA with mild OPCA had many GCIs in the cerebellar white matter (corresponding to our group 1), and that three cases with severe OPCA had a few GCIs in the cerebellar white matter (corresponding to our groups 3 or 6). Arai et al. [4] found many GCIs in the cerebellar white matter of a case with Shy-Drager syndrome (corresponding to our group 1) and few in a case with dominant OPCA (corresponding to our group 3), supporting our findings. Nakazato et al. [18, 19] described many GCIs in cases with severe OPCA pathology, but such cases did not show severe devastation of the cerebellar white matter, thus corresponding to our groups 2 or 5. Costa et al. [8] presented a case with severe OPCA that had a few GCIs in the cerebellar white matter (corresponding to our group 3). This tendency was in accordance with other previous reports [1, 2, 14, 23, 24]. In most cases in which few GCIs were seen, the cerebellar white matter exhibited sponge-like gliosis [1, 2]. In sponge-like gliosis, which is distinct from isomorphic (compact) gliosis, the sponge-like appearance of the tissue is due to severe disruption of the structure, which consists of loose networks of glial fibers with only a few astrocytes, and which has totally lost its neuronal parenchyma including oligodendrocytes. The size of GCIs was smaller in cerebellar white matter with this type of gliosis than in that with mild or isomorphic gliosis (Fig. 1d, g).

For the corticopontine tract, known to be one of the commonly affected regions in MSA [1, 29] and a predilection site for GCIs [1, 4, 18, 23], previous reports have shown that the incidence of GCIs in this site varies from many [23] to few [4]. In this study, only a few GCIs were found in the cases with mild OPCA. The incidence of GCIs tended to increase in correlation to the severity of OPCA. The more severe OPCA becomes, the greater is the loss of nerve fibers, although they do not disappear completely [29]; however, GCIs remained frequent even in cases with severe OPCA. The incidence of GCIs here did not depend upon the degree of SND. This result is in accordance with those of previous reports [1, 4, 18, 23].

In the pyramidal tract, a few GCIs were found in the cases with minimal OPCA and SND. In the cases with severe OPCA or SND, the number of GCIs increased in correlation with the severity; the highest frequency of GCIs was seen in the group 6 showing both severe OPCA and SND, in accordance with previous reports [4, 10, 16, 18, 23] This correlation was also seen for the internal capsule. In the cerebral white matter, corpus callosum and anterior commissure, a similar tendency for the incidence of GCIs was seen, although fewer GCIs were found.

The putaminal lesions have been reported to be more severe in the dorsolateral than in frontomedial regions [14, 23] and to have a positive association between their neuronal loss and incidence of GCIs [19]. However, less attention has been paid to the pencil fibers in the putamen than to the putamen itself [24]. In these bundles, the number of GCIs seemed to be related to the degree of SND, especially to the degree of the severity of lesions in the putamen rather than in the substantia nigra, but not to the degree of OPCA. Only few GCIs were seen in groups 1–3 with mild SND; whereas in cases with severe SND (groups 4–6), the number of GCIs seemed to increase. The pencil fibers were well preserved even in the severe cases of SND, and no decrease in the number of GCIs was observed. In other lesions, the incidence of GCIs varied from case to case, and from group to group, and seemed to be independent of the severity of OPCA, SND, or both.

The significance of GCIs remains unsettled. It is a matter of dispute whether the existence of GCIs is a primary or a secondary change in MSA, although GCIs are widely distributed even in the regions in which neuropathological changes seem negligible or minimal [7, 24]. The findings

in the cerebellar white matter may offer a clue to answering this question. GCIs appear in the cerebellum of cases with minimal OPCA and those with SND in which OPCA is not histologically apparent, suggesting that the existence of GCIs may represent an early change in MSA and may be a useful neuropathological hallmark for diagnosing MSA. In addition, it underlines the possibility that the presence of GCIs represents a primary change in the cerebellar white matter, although some changes that cannot confirmed by light microscopy might precede the appearance of GCIs.

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