Commentary

Multiple System Atrophy

Clues from Inclusions

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Multiple system atrophy (MSA) was added to the list of neurodegenerative diseases defined by cytoplasmic inclusions when Papp et al¹ demonstrated specific oligodendroglial inclusions, referred to as glial cytoplasmic inclusions (GCIs), in brains of patients affected by MSA. Their observation has since allowed more accurate interpretation of the pathological differential diagnosis of parkinsonian, cerebellar, and autonomic disorders and has further supported the concept of MSA as an entity. Moreover, MSA appears unique among neurodegenerative diseases in that its hallmark inclusion affects oligodendrocytes, suggesting that glial changes and glial-neuronal interactions may be early events in neurodegeneration, and emphasizing the potential importance of myelin metabolism in disease pathogenesis. In the current issue of this journal, Matsuo and colleagues² expand on this finding by providing evidence that myelin degeneration in patients with MSA is more widespread than previously recognized.

Development of the Multiple System Atrophy Concept: Historical Perspective

MSA is a sporadic neurodegenerative disease encompassing three previously described clinical syndromes—striatonigral degeneration (SND), olivopontocerebellar atrophy (OPCA), and Shy-Drager syndrome (SDS)—with a common pathology.³ The current view of MSA, however, took a number of years to unfold and is probably best understood from a historical perspective.

In 1900, Déjerine and Thomas introduced the term olivopontocerebellar atrophy (OPCA) when they described two middle-aged patients with an ataxic disorder and pathological changes in the brainstem and cerebellum. The striatum and substantia nigra were not examined, or at least not commented on.⁴ Déjerine and Thomas, and later Loew⁵ under the tutelage of Déjerine himself, recognized OPCA cases as “atypical” when they had a hereditary component or, interestingly, when there

were associated CNS lesions, but their concept of “atypical OPCA” fell quickly into disuse.⁶ Nevertheless, OPCA as described by Déjerine and Thomas persisted as an entity and was the subject of a number of studies in the middle part of the 20th century^{7,8} despite the fact that the distinction between familial and sporadic OPCA (see below) and the frequency of associated lesions were not fully appreciated.

In 1960, Shy and Drager described a neurological syndrome with autonomic failure and parkinsonism, SDS,⁹ in which striking orthostatic hypotension was the common clinical feature. Previously described cases of orthostatic hypotension, in retrospect, may have represented SDS,^{10–12} but these were not as well characterized. Shy and Drager noted degeneration of the intermediolateral cell columns of the spinal cord (later recognized as the anatomical substrate of autonomic failure), in addition to neuronal loss and/or gliosis at many other sites including the caudate nuclei, substantia nigra, cerebellar Purkinje’s cells, and inferior olivary nuclei. Lewy bodies were noted in a minority of the early SDS cases, raising the possibility of “transitional” forms between SDS and Parkinson’s disease,¹³ although it should be noted that examination of the striatum and (now) the presence of GCIs will usually permit distinction between these two apparently separate processes. It is also important to remember that the description of SDS (as well as SND) preceded the availability of levodopa for diagnosis and treatment of parkinsonism.¹⁴

The year before, van der Eecken et al had presented “Striopallidal-nigral degeneration: An hitherto undescribed lesion in paralysis agitans” to the American Association of Neuropathologists. Their account was published in 1960 and then described in more detail in 1961 and 1964 under the designation “striatonigral degeneration” (SND).^{15–17} SND patients typically exhibited parkinsonism and the major foci of neuronal loss were in the striatum and the substantia nigra. Lewy bodies were not

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a constant feature in SND, being present in the substantia nigra in only one of four cases. OPCA was also described in one case but, as in SDS, only in retrospect was OPCA found to be an important component of the underlying disease. It also seems surprising that striatal pathology in patients with parkinsonism was not described until the early 1960s. In fact, pathological accounts of typical SND were described earlier, but were included under the label of Parkinson's disease.¹⁸ Given that approximately 10% of patients with parkinsonism have MSA, it is indeed likely that many such cases "have swelled the ranks of Parkinson's disease clinics"¹⁴ unrecognized as a separate disease.

Finally, in a 1969 paper titled "Orthostatic Hypotension and Nicotine sensitivity in a Case of Multiple System Atrophy," Graham and Oppenheimer reported the case of a 60-year-old man who presented with clinical features of SDS as well as cerebellar ataxia exacerbated by cigarette smoking.¹⁹ Progressive clinical deterioration ensued and he died about 2 1/2 years later. Neuropathological examination disclosed degeneration of the striatum, substantia nigra, pons, inferior olivary nucleus, cerebellar Purkinje's cells, and intermediolateral cell column of the spinal cord. From careful examination of this single case and review of pertinent literature, Graham and Oppenheimer made the observation that SDS, SND, and OPCA often co-existed clinically and pathologically and were likely different expressions of one underlying disease. For better or worse, they introduced the term "multiple system atrophy" for this group of diseases to avoid "unnecessary confusion caused by inventing new names."

Clinical Neuropathology and Patterns of Degeneration

According to current understanding, almost all MSA patients develop parkinsonism or cerebellar signs. Thus, about 80% of patients are parkinson-predominant (SND-predominant) and 20% are cerebellar-predominant (OPCA-predominant).²⁰ Pure SND is relatively common clinically, whereas pure OPCA is unusual. Onset of autonomic dysfunction (SDS) in MSA is variable but is usually present at some point during the disease course. Patients with severe autonomic dysfunction tend to be younger and to have a shorter survival.²⁰ As alluded to previously, the frequent occurrence of parkinsonism emphasizes the often difficult distinction between MSA and disorders such as Parkinson's disease and progressive supranuclear palsy (Steele-Richardson-Oslewski syndrome).

Descriptions in recent studies of patterns of pathological involvement of gray matter are generally an extension of the original accounts, noting neuronal loss and gliosis in the striatum (more in the putamen than in the caudate nucleus), substantia nigra, locus ceruleus, inferior olivary nucleus, pontine nuclei, cerebellar Purkinje's cells, intermediolateral cell column in the thoracic spinal cord, and Onuf's nucleus in the sacral spinal cord. Other populations variably affected include the external pallidum, thalamus, vestibular nuclei, dorsal motor nucleus of the va-

gus, and corticospinal tracts.²⁰⁻²² The degree of involvement tends to follow clinical signs, with the striatonigral system severely affected in parkinson-predominant and pure SND cases, and the olivopontocerebellar system severely affected in cerebellar-predominant cases.²⁰ Pathological changes in the olivopontocerebellar system may be subtle or nonexistent in pure SND cases, but because pure OPCA is unusual, striatal and nigral pathology is present in the majority of MSA cases. Autonomic dysfunction in MSA is related to degeneration of the intermediolateral cell column and Onuf's nucleus.¹³ Dementia, on the other hand, is not a major presenting problem, although some cortical deficits emerge with psychometric testing²³ and subtle pathological abnormalities affecting the cerebral cortex are described.^{24,25}

Absence of Well-Defined Genetic Etiology

MSA is a largely sporadic condition and there have been few studies investigating potential genetic etiologies. In a recent study of 80 well-characterized MSA patients, Bandmann et al²⁶ found no alterations in either the SCA-1 or SCA-3 gene, indicating that MSA is likely distinct from autosomal dominant ataxias associated with unstable trinucleotide repeats.²⁷ Gotoda et al²⁸ identified a mutation in the gene for α -tocopherol transfer protein in one patient with adult-onset spinocerebellar dysfunction, substantiating the notion that altered vitamin E metabolism leads to spinocerebellar pathology; however, the patient's neurological disorder more closely resembled Friedreich's ataxia than MSA. In a case-controlled study, Nee et al²⁹ found that patients with MSA had significantly more potential exposures to metal, dusts, fumes, plastic monomers and additives, organic solvents, and pesticides than the control population. The authors concluded that MSA develops as a result of a genetically determined selective vulnerability in the nervous system, although the nature of the selective vulnerability was not elucidated and no disease-associated genetic locus was identified. It should also be emphasized here that, aside from one report of GCIs in SCA-1 pathology,³⁰ GCIs continue to represent a specific hallmark of sporadic MSA and are generally not a component of the inherited ataxias. Therefore, the available data indicate that MSA is an acquired condition distinct from CNS diseases with well-defined genetic causes. In this regard it is interesting to note that increased amounts of iron are consistently found in the striatum of MSA patients both neuropathologically and on neuroimaging.^{31,32} Fe(II) as a potent catalyst of reactive oxygen species has been implicated in the pathogenesis of common neurodegenerative diseases.^{33,34} At present, evidence for oxidative stress in MSA remains circumstantial.

Glial Cytoplasmic Inclusions as the Pathological Hallmark of Multiple System Atrophy: Characteristics, Distribution, and Pathogenic Implications

In their original study in 1989, Papp et al documented the important finding of argyrophilic oligodendroglial inclu-

sions in the brains of patients with MSA.¹ The GCIs were first noted by Gallyas silver impregnation, used to demonstrate Alzheimer's neurofibrillary pathology; they were localized largely to the white matter and to cells with morphological features of oligodendrocytes in all 11 cases. Neuronal inclusions with similar characteristics to GCIs were also reported,³⁵ but these are now considered insufficient in density or specificity to be a reliable feature of MSA.³⁶ No GCIs were seen in any of the age-matched normal controls and GCIs were absent from a variety of other neurodegenerative diseases. Subsequent studies have verified the presence of GCIs in MSA as well as the conclusion of Papp et al that GCIs are sensitive and specific hallmarks of MSA.³⁷⁻⁴² The relevance of GCIs, not only to characterizing a nosological entity but also in terms of enhancing neuropathological interpretation of parkinsonian, ataxic, and autonomic disorders, is self-evident.

By routine light microscopy, GCIs are faint eosinophilic inclusions that eccentrically displace the nucleus. The Gallyas silver technique produces selective dark staining of inclusions with a clean background, making it more useful in demonstrating GCIs than Bodian or Bielschowsky techniques, which have more background and less pronounced staining of the inclusion. The various silver techniques show GCIs are sickle-shaped to flame-shaped to ovoid, sometimes superficially resembling neurofibrillary tangles. The fact that GCIs were not detected earlier, though somewhat surprising, may reflect their less intense staining with commonly used silver impregnations and the fact that GCIs are essentially negative with other common stains, including phosphotungstic acid hematoxylin, periodic acid-Schiff, Masson trichrome, Alcian blue, thioflavine S, Congo red, oil red O, or Sudan black B.^{3,36} On ultrastructural examination, GCIs are comprised of loosely aggregated filaments with cross-sectional diameters of 20 to 30 nm. The filaments often entrap cytoplasmic organelles such as mitochondria and secretory vesicles, have no limiting membrane, and are reported to have tubular profiles and electron-dense granules along much of their length.^{36,39} By immunocytochemistry, GCIs are consistently positive for ubiquitin and α -B crystallin, and less intensely positive for α - and β -tubulins.^{3,36} Ubiquitin and α -B crystallin positivity is not surprising, as both proteins accumulate in a variety of poorly soluble inclusions as a general indicator of cellular stress. MAP5 positivity is also reported.^{38,39} GCIs are negative for neurofilaments, glial fibrillary acidic protein, myelin basic protein, vimentin, actin, desmin, myosin, and cytokeratin. The variable literature on tau immunocytochemistry may reflect the phosphorylation state of the tau epitope, as GCIs are generally negative for phosphate-dependent tau antibodies and positive for normal adult tau;⁴³ this is in contrast to the neurofibrillary pathology of Alzheimer's disease. The apparent absence of phosphorylated tau further distinguishes GCIs from glial lesions in corticobasal degeneration and progressive supranuclear palsy (eg, tufted astrocytes, coiled bodies, astrocytic plaques).^{36,43}

The regional distribution of GCIs within the brain is complex. Significant numbers of GCIs have consistently

been found in the putamen, pallidum, lateral caudate nucleus, basis pontis, spinal cord intermediate gray matter, internal capsule, and middle cerebellar peduncle,³⁶ indicating a general tendency for GCIs to accumulate in and around degenerated brain regions. Not surprisingly, some have viewed this as evidence that GCI formation is a secondary phenomenon. On the other hand, Papp and Lantos found from their distribution study that GCIs preferentially involve suprasegmental motor systems, supraspinal autonomic systems, and their targets, while sparing primary sensory areas and cortical and subcortical limbic structures, suggesting a "system-bound" oligodendroglial degeneration.³⁵ Moreover, the presence of GCIs in such areas as motor cortex, cerebellar white matter, subthalamic nucleus, and brainstem reticular formation (structures that do not typically degenerate in MSA) and their relative absence in the substantia nigra, locus ceruleus, and inferior olivary nucleus suggest that GCI formation cannot be attributed solely to a reaction to neuronal damage.³⁵ Inoue et al⁴⁰ also found a general relationship between the density of GCIs and the severity of white matter tract involvement, although again GCIs were more widespread than neuronal loss and the density of GCIs in the cerebellar white matter in relation to severity of pathology was more complex. Few GCIs were found in cerebellar white matter with severe OPCA, whereas numerous GCIs were sometimes found with little or no OPCA, furthering the argument that GCIs may be an early lesion and not necessarily a reaction to neuronal injury.

The Oligodendrocyte and Myelin as Potential Primary Targets

GCIs consistently localize to cells with oligodendroglial characteristics. By immunocytochemistry, GCI-containing cells are immunoreactive with antibodies against Leu-7, carbonic anhydrase enzyme II, and transferrin.^{39,42} Ultrastructural characteristics of GCI-containing cells are also consistent with oligodendroglial origin.^{1,37,39,42} As mentioned, oligodendroglial inclusions are rarely encountered in other neurodegenerative diseases; only in MSA does the oligodendrocyte represent the predominant inclusion-bearing cell. It is somewhat paradoxical that MSA rather eloquently affects selected gray matter "systems" whereas its hallmark inclusion-bearing cell produces myelin. Implicating the oligodendrocyte as the primary target, therefore, means providing a mechanism for region-specific oligodendrocyte dysfunction or a mechanism whereby oligodendrocyte dysfunction leads to pronounced destruction of selected vulnerable neuronal populations. To date there is little evidence that oligodendrocytes may be subtyped according to the neuronal populations they subserve. Older classifications of Mori and LeBlond⁴⁴ and Stensaas and Stensaas⁴⁵ subtyped oligodendrocytes based on fine structural features of the oligodendrocyte nucleus and processes and myelin sheaths, respectively, providing indirect evidence for functional specialization, but no conclusive evidence for tract specificity. More recently,

oligodendrocyte development has been characterized by immunophenotype, shedding some light on the development of macroglia, but likewise has not progressed to the point of tract or functional specificity.⁴⁶ Additionally, single oligodendrocytes have been shown to myelinate axons of different anatomical tracts, casting some doubt on the possibility that oligodendrocytes may be classified based on the functional properties of corresponding axons.^{47,48} In MSA, GCI is reported to involve so-called perivascular, perifascicular, and perineuronal oligodendrocytes without further qualification as to subtype. In essence, then, GCIs involve all morphological types of oligodendrocytes with varying frequency in various anatomical regions.^{3,35} It therefore appears that oligodendroglial disturbance in MSA, whether or not it occurs primarily, tends to be more generalized and would likely have to occur in conjunction with intrinsic vulnerability of selected neuronal populations, the nature of which remains to be determined.

In the current issue of this journal, Matsuo and colleagues² document extensive myelin degeneration in MSA brains by demonstrating widespread white matter (but not GCI) immunopositivity with anti-EP antisera and monoclonal antibody QD-9. Both antibodies recognize synthetic peptide QDENPVV (corresponding to human myelin basic protein residues 82–88) and were previously shown to immunolabel degenerated myelin in multiple sclerosis and infarcted brains, but not myelin in normal brain.⁴⁹ The presence of unusual myelin basic protein epitopes in MSA, in both affected and unaffected brain regions, substantiates the notion of widespread oligodendroglial dysfunction in MSA and highlights white matter disease as an integral component. Nevertheless, the question of how oligodendrocyte degeneration might lead to neuronal loss, to the extent encountered in MSA, remains. It is noteworthy in this regard that axonal damage is known to occur in otherwise classical demyelinating conditions.^{50,51} Furthermore, the critical trophic influences that are described between oligodendrocytes and axons⁵² indicate that oligodendroglial pathology would likely affect neuronal function. Oligodendrocyte pathology in the form of (presumably chronic) inclusions, on the other hand, causing selective and severe gray matter damage, would be unusual. It is safe to conclude that despite the compelling evidence presented so far, more studies are needed before GCIs or degenerated myelin epitopes may be interpreted as primary lesions in the neurodegenerative process of MSA.

Inclusions: Etiology Versus Epiphenomenon

The difficulty in establishing a direct association between inclusions and etiology is not unique to MSA. While inclusions provide empirical pathological hallmarks for a number of neurodegenerative diseases and are particularly strategic for studying disease pathogenesis,^{53,54} a direct association between inclusion and etiology (as opposed to epiphenomenon) remains unproven for most neurodegenerative disorders. This includes neurofibrillary pathology of Alzheimer disease and progressive supranuclear

palsy, Lewy bodies of Parkinson's disease and diffuse Lewy body disease, Pick's bodies of Pick's disease, the various tau pathologies of corticobasal degeneration, and Rosenthal fibers of Alexander's disease. On the other hand, recent reports demonstrating tau gene mutation in familial multiple system tauopathy,⁵⁵ and the immunolocalization of α -synuclein, a protein mutated in chromosome 4-linked familial Parkinson's disease,⁵⁶ to Lewy bodies of idiopathic Parkinson's disease,⁵⁷ provide direct links between genetic lesions and abnormal gene products accumulating in hallmark inclusions. Therefore, as the biochemical composition of GCIs and associated myelin abnormalities continue to be elucidated, rigorous study of the pathological lesions of MSA, with the hope of determining etiology and treatment strategies, appears warranted. This is particularly true in light of the lack of a genetic basis for the disease.

Conclusions

After nearly a century of study MSA is now known to be a specific, albeit heterogeneous, neurodegenerative disease encompassing olivopontocerebellar atrophy, striatonigral degeneration, and Shy-Drager syndrome. It was through thoughtful case examination, detailed neuropathological study, and advances in molecular genetics that the entity of MSA was fully realized. The relatively recent identification of unique cytoplasmic inclusions and widespread white matter abnormalities have broadened the scope of the neurodegenerative process, and have challenged traditional views of MSA as a disease primarily of gray matter. While studies on GCIs and oligodendroglial dysfunction will continue to provide insight into the pathophysiology and perhaps etiology of MSA, the progress already made will continue to be an important lesson in neurodegenerative disease pathogenesis and careful clinicopathological observation.

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