Progressive Supranuclear Palsy

Roger C. Duvoisin, Lawrence I. Golbe and Frederick E. Lepore

ABSTRACT: Progressive supranuclear palsy (PSP) was first recognized as a distinct morbid entity by Richardson, Steele and Olszewski a quarter century ago. Subsequent experience has confirmed and extended their original observations. PSP has become familiar as a chronic progressive disorder with extrapyramidal rigidity, bradykinesia, gait impairment, bulbar palsy, dementia and a characteristic supranuclear ophthalmoplegia. It is an important cause of parkinsonism. Its etiology remains obscure. Familial concentrations have not been observed.

Some cases exhibit no oculomotor dysfunction. Dementia is usually mild. Recent neuropsychological studies have defined features consistent with frontal lobe cortical dysfunction. Seizures and paroxysmal EEG activity may occur.

CT and MRI scans show midbrain atrophy early and later atrophy of the pontine and midbrain tegmentum and the frontal and temporal lobes. PET scans have shown frontal hypometabolism and loss of striatal D-2 dopamine receptors. Postmortem studies have documented involvement of both dopaminergic and cholinergic systems. Treatment remains palliative and unsatisfactory.

Nearly 25 years ago, at the June 1963 meeting of the American Neurological Association, the late J.C. Richardson read a paper describing the clinical features of eight patients who had presented a "common syndrome of ocular, motor and mental symptoms". All had "defects of ocular gaze, spasticity of the facial musculature with dysarthria and sometimes dysphonia, extensor rigidity of the neck with head retraction and dementia". Six of these patients had been studied postmortem by Steele and Olszewski. The salient findings comprised marked neuronal degeneration in the midbrain and pontine tegmentum, the substantia nigra, subthalamic nucleus and pallidum with argyrophilic neurofibrillary tangles in the affected areas. Despite the dementia, the cerebral cortex appeared to be spared.

The discussion which followed the presentation remained of interest today. The first discussant, H. Houston Merritt, urged the authors to search for a toxic etiology. Kurland noted the similarity to the parkinson-dementia complex of Guam which he suspected was due to the ingestion of a toxic ingredient of the plant Cycas circinalis. Other discussants noted similarities to post-encephalitic parkinsonism and to Creutzfeldt-Jakob disease.

Richardson and his colleagues recognized the similarity of their patients to Verhaart's case as well as to those reported by Chavany, and Neuman and initially employed Verhaart's term "heterogenous system degeneration" to designate the disorder. In the full account published the following year Steele et al changed the name to "progressive supranuclear palsy". This designation, though not fully satisfactory, gained general acceptance and has supplanted the eponymous designation Steele, Richardson, Olszewski syndrome which has also been widely used.

The condition soon became familiar to neurologists as a particular disorder characterized clinically by a chronic progressive course, extrapyramidal rigidity, axial dystonia, dementia, a pseudobulbar palsy and a supranuclear ophthalmoplegia chiefly affecting vertical gaze. Pfaffenbach et al in a paper published in


From the Department of Neurology, University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, New Brunswick, New Jersey
Reprint requests to: Dr. Roger C. Duvoisin, Department of Neurology, UMDNJ - Robert Wood Johnson Medical School, CN-19, New Brunswick, NJ 08903 USA

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and the frequent onset with gait disturbance, perhaps respond most frequently and consistently among populations of Parkinson’s disease. The presentation of an akinetic-rigid parkinsonism by “any of the numerous neurologists” who examined them. They noted the absence of tremor, a flexed attitude or of parkinsonian posturing of the hands in their patients. Associated movements were preserved and blinking was “more frequent.”

In contrast to these early views, PSP has been encountered most frequently and consistently among populations of Parkinson’s patients. The major differential diagnosis has been idiopathic parkinsonism. The presentation of an akinetic-rigid parkinson syndrome, atypical due to the infrequent presence of tremor and the frequent onset with gait disturbance, perhaps responding to levodopa therapy for a year or two, then rapidly losing the response and eventually declaring itself with the advent of the characteristic supranuclear ophthalmoplegia has become quite familiar in movement disorder clinics.

PSP has been identified on average in various clinical series in about 4% of cases of parkinsonism. Jackson et al23 reported that their 16 cases of PSP represented 3.9% of their parkinson clinic population. Stern and Hurtig24 have noted a prevalence of 3.5% among their parkinson patients. Agid et al25 report that 7% of the patients admitted to their hospital with the diagnosis of parkinsonism must be essentially spared, but modern neuroimaging has shown that cerebral atrophy, predominantly frontal and temporal, is not unusual. Scattered case reports over the years have documented additional clinical features such as myoclonus26 and sleep disturbances.21,22

**PSP and parkinsonism**

While they admitted the presence of features which in the earlier stages of the disorder could lead “one to wonder if the case would progress to parkinsonism”, Steele et al6 stated that none of their cases had been considered to represent parkinsonism by “any of the numerous neurologists” who examined them. They noted the absence of tremor, a flexed attitude or of parkinsonian posturing of the hands in their patients. Associated movements were preserved and blinking was “more frequent.”

The mean duration of PSP before diagnosis in Kristensen’s review of 325 cases collected from the literature was 3.9 years.7 In the recent study of 50 cases by Golbe et al,8 the interval was 4.9 years. Maher and Lees in a similar study noted a mean interval between onset and diagnosis of 3.6 years.7 The 44 cases culled by Pfaffenbach from the Mayo Clinic files were diagnosed on average approximately 4.5 years after symptom onset. Thus we may accept a conservative estimate of a mean 4-year delay between onset of symptoms and diagnosis.

The mean survival of deceased patients in years after onset in recent series has been 5.7 in 73 cases reviewed by Kristensen,7 6.9 in the cases studied by Golbe et al8 and 5.9 in Maher and Lees’ cases.9 If we accept six years as the mean duration of survival after onset and four years as the mean interval from onset to diagnosis, then we may conclude that only one third of the cases of PSP among our parkinson patients are actually identified. Thus the true prevalence of PSP among patients diagnosed on clinical grounds as having parkinsonism must be in the neighborhood of 12%.

We should add to this group of patients the cases of PSP who fail altogether to develop the typical ophthalmoplegia and thus are not diagnosed at all except as an unexpected finding at autopsy. The numerical importance of these atypical cases of PSP is unknown. They may only account for an additional 1% or 2% of our parkinsonian patients but even without them, PSP emerges as the second most important cause of parkinsonism today, exceeded only by Parkinson’s disease.

**Epidemiology**

The gradually increasing recognition of PSP by clinical neurologists begs the question whether the disease is actually becoming more prevalent. Epidemiological data adequate to assess that possibility are not presently available. The first epidemiological survey of the disorder was attempted this past year. Using the records of practicing neurologists, nursing homes and a tertiary care movement disorder center, Golbe et al9 found the prevalence ratio of PSP in two central New Jersey counties to be 1.39/100,000 population without significant sex difference. Since it is clear from the above discussion that only a portion of the cases prevalent among a given population are likely to be recognized, this figure represents a low estimate.

We know from clinical experience that some PSP patients present with dementia as the predominant manifestation and are misclassified as Alzheimer’s disease, multi-infarct dementia or something else. The number of these cases is difficult to estimate from data presently available. They may prove on future study to be even more numerous than those presenting with parkinsonism. Thus the cases of PSP recognized today represent only the “tip of an iceberg” whose full extent remains unknown.

The original cases of Steele et al6 were all male, but their patients were largely drawn from a veterans’ hospital. Subsequent series of cases have contained a more modest preponderance of males. Kristensen in her review noted that of 302 cases in which sex was reported, 60% were men. However, more recent data suggests that there is no significant sex difference. The data of Golbe et al9 and of Maher and Lees,9 the two most recent large series of cases, comprise together 102 patients. There were 51 men and 51 women.

The evolution of the disease was assessed retrospectively in the two studies cited above. The age of onset was about 62 years.
years. The most common initial symptom was gait disturbance; it occurred a mean of 1.9 years after disease onset and was the initial symptom in 62% of the patients. Progression to total disability is more rapid than in untreated Parkinson’s disease. The mean interval from initial symptom to confinement to bed or wheelchair is only 5.8 years. The most characteristic symptom, visual difficulty, occurred relatively late at a mean of 3.7 years after disease onset.

The cause of PSP remains utterly obscure. No convincing familial occurrence or geographic, ethnic or temporal clusters have been reported. The pathological anatomy and chemistry have thus far offered no clues. Davis et al29 recently performed a case-control study of 50 factors known or suspected of being associated with other neurodegenerative disorders including head trauma, stroke, thyroid disease, nonsmoking and exposure to animals, pesticides and well water. The only statistically significant finding was that patients with PSP were more likely than controls to have lived in a rural area during adulthood. Whether this reflects case ascertainment bias or an etiological overlap with Parkinson’s disease must await further study.

Oculomotor Dysfunction

Steele et al5 had noted “loss of conjugate vertical gaze to command and in following and attraction movements”. The supranuclear character of this disorder of ocular motility was indicated by the observation that the eyes moved fully “when the gaze was fixed and the head passively moved”. Subsequent studies of the oculomotor defects carried out by Newman et al,27 Dix et al,28 Troost and Daroff29 and many others have uniformly confirmed and extended the original observations.

The characteristic supranuclear ophthalmoplegia remains the pathognomonic clinical sign of the disease. The diagnosis may be suspected but cannot be established in its absence. The initial vertical gaze deficit is hesitation on looking downward. We have been impressed by the variability of this deficit in its initial stages. It may be noted on one examination but not on another an hour later. Often, the patient’s family seem to be aware of the problem before we can find an objective abnormality on examination. They note that the patient has difficulty maintaining eye contact during conversation and in the performance of tasks requiring downgaze.

Later, hypometric saccades may be noted. Eventually, the saccadic palsy is apparent on upward and lateral gaze. Fixation is impaired by the intrusion of brief transient jerks which move the eyes abruptly ½ to 3° from the point of fixation. Smooth pursuit has a “cogwheel” or “jerky” quality, the patients being unable to match eye velocity to target velocity. The vestibulo-ocular reflex is hyperactive. This phenomenon is readily demonstrated by testing the ability of the patient to maintain fixation on a target rotating with the head, for example the tip of the handle of a Gowers reflex hammer whose tire is held firmly on the forehead (Figure 1). Poor suppression of the vestibulo-ocular reflex is especially marked in PSP cases when the head is moved downward.

Bell’s phenomenon may be preserved in the presence of significant ophthalmoplegia but is lost in advanced stages of the disease. Eventually nuclear ophthalmoplegia ensues and the eyes fail to respond to any gaze strategy or reflex ocular movement.

A variety of disorders of eyelid motility may be observed. Spontaneous blinking is profoundly reduced. In a recent study, Golbe et al30 found a mean blink rate of 3.5 per minute in PSP patients. This is much lower than the mean rate of 11 per minute found by Karson31 in untreated Parkinson’s disease. Karson documented a mean of 20 blinks per minute in normal subjects.

PSP patients may be unable to open their eyes due to blepharospasm or the involuntary inhibition of levator function.22 Goldstein and Cogan32 retained the term “apraxia” of lid opening used in the earlier literature24 to denote this phenomenon. Conversely, the patients may be unable to close their eyes voluntarily due to “apraxia” or supranuclear paralysis of eye closure. Golbe et al30 found various combinations of blepharospasm, involuntary levator inhibition and “apraxia” of lid closure in 5 of 38 patients. These supranuclear disturbances of eyelid function occurring in combination are in our experience much more prominent in PSP than in other extrapyramidal disorders and a major cause of disability in some cases.

PSP patients frequently complain of greater degrees of visual disability than patients with ophthalmoplegias of other etiologies. It is tempting to relate their complaints to the degeneration of the superior colliculus, which is a striking feature of the disease. The superior colliculus has a dorsal portion serving as a sensory reception area for direct retinal input and a ventral portion serving as a motor structure projecting to the subthalamus and brainstem. It has been shown capable of providing the visual input necessary for accurate guidance of saccades in primates with lesions of the striate cortex.35 Thus loss of collicular visual processing may help explain the distinctive visual deficits in these patients. This hypothesis is consistent with the observation that the diameter of the quadrigeminal plate cistern as observed on CT scans correlates with the clinical severity of the oculomotor deficits.36

It is interesting to compare the oculomotor deficits of PSP with those of Parkinson’s disease, olivopontocerebellar atrophy and other forms of multiple system atrophy. Although decreased frequency of eyeblink, diminished excursion of upward gaze and “cogwheeling” of smooth pursuit may be observed in Parkinson’s disease, the abnormalities are much milder and are observed chiefly in advanced stages of the disease. Frank paresis of gaze occurs rarely and then only in exceptional circumstances. Guiloff et al,37 for example, reported transient supranuclear ophthalmoplegia in two patients with Parkinson’s disease during intercurrent infections.

Similar oculomotor deficits occur in olivopontocerebellar atrophy38 and these may complicate its diagnostic differentiation from PSP.39 In general, horizontal gaze is more markedly impaired in OPCA and vertical gaze in PSP. Moreover, the compensatory headthrust employed by OPCA patients to bring their eyes on target has not been observed in PSP perhaps because the nuchal rigidity of PSP prevents it.

Epileptic Seizures

Although seizures were observed in three of Steele et al’s eight cases5 the occurrence of seizures in PSP has received little attention. Only two other cases have been described19,20 but Nygaard and Duvoisin recently found that seizures had occurred in seven of 55 PSP patients whose records they had reviewed.40 This is a much higher incidence than could be expected by chance. They occurred early as well as late in the clinical course. The clinical manifestations included recurrent episodes of altered awareness, loss of consciousness, nocturnal convuls...
Figure 1 — A simple technique for assessing suppression of vestibulo-ocular reflex (VOR) with Gowers reflex hammer. Normal subject will suppress the VOR and maintain eyes fixed on the tip of the handle as examiner moves the patient's head laterally or vertically.

Seizures do not seem to be a prominent feature of PSP. They tend to be mild and to recur infrequently. Thus they may often be overlooked. However, since seizures are extremely rare in Parkinson's disease⁴¹ their occurrence and/or the finding of paroxysmal activity on EEG may aid in the diagnostic recognition of PSP.

Stroke

PSP appears more likely than Parkinson's disease to be associated with radiographic evidence of stroke.⁴² However, the study of Davis et al.²⁶ failed to find a greater prevalence of stroke in PSP patients than in age-matched controls. The prevalence of stroke may be lower in Parkinson's disease than in the general population. It is also possible that cerebral vascular disease may rarely produce a clinical syndrome resembling PSP. Further study of a possible angiopathy associated with PSP may be warranted but even if one is found, the direction of causality will need to be clarified.

Neuroimaging

Because of the difficulty of early diagnosis and especially of diagnosis in patients lacking the characteristic deficits of ocular
motility, it would be useful if the gross anatomical features of PSP could be identified radiologically early in the course of the illness. The brainstem atrophy had been shown on pneumoencephalography and can be seen on computerized tomographic (CT) scans. Several studies of CT scans in PSP have confirmed the findings of atrophy of the midbrain tegmentum, superior colliculi, pons and temporal lobes. Generalized cerebral sulcal atrophy and ventricular enlargement with widening of the interpeduncular and quadrigeminal plate cisterns can be seen. The third ventricle shows more marked widening posteriorly.

In a study of 17 patients, some studied serially, Schonfeld et al showed that a minor change present early was decreased anterior-posterior diameter of the midbrain. In all but the earliest cases the anteroposterior diameter of the midbrain was less than 15 mm. Normals measured 18 ± 1.3 mm. With progression of the disease, atrophy of the pons and midbrain, visualization of the aqueduct and dilatation of the quadrigeminal plate cistern became apparent. In clinically more advanced stages they saw dilatation of the aqueduct, progressive dilatation of the 3rd and 4th ventricles and atrophy of the temporal lobe. A correlation was found between the degree of oculomotor paresis and widening of the quadrigeminal plate cistern. There was also a correlation between the overall clinical severity of the disease and the mean of the midbrain and pontine diameters.

These changes have in our experience proven helpful in distinguishing PSP from OPCA. Small midbrain diameters have not been seen in OPCA. Atrophy of the cerebellum is obvious in OPCA even before obvious clinical cerebellar signs can be demonstrated but occurs only late in PSP if at all. Pontine atrophy is seen early in OPCA but only late in PSP when the diagnosis is clinically obvious.

The clearer visualization of infratentorial structures yielded by magnetic resonance imaging promises to render this imaging technique especially useful in diagnosing PSP. Whether the recent demonstration of signal loss in the superior colliculi, nigra and putamen ascribed to the paramagnetic effect of iron deposition will aid in the diagnosis of PSP, as suggested by Drayer et al, remains to be seen.

Positron emission tomography (PET) studies with 2-deoxyglucose have shown marked hypometabolism in the frontal and temporal regions. This finding contrasts with the parietal pattern of hypometabolism found in Alzheimer’s disease. PET studies using the D-2 dopamine receptor ligand Br25 bromopipероне have shown a marked loss of the D-2 receptor sites in the striatum. One would expect similar findings in striatonigral degeneration but not in Parkinson’s disease. Fluorodopa PET studies have shown as expected a loss of striatal dopamine metabolism. Whether fluorodopa PET studies can discern differences in regional patterns of striatal dopamine metabolism between PSP and Parkinson’s disease paralleling the differences observed in post-mortem studies of striatal dopamine depletion in these two conditions remains to be determined.

Dementia

Dementia was a feature in seven of the nine patients reported by Steele et al but with subsequent experience it has proven to be less constant and milder than had initially been thought. The severe bulbar palsy present in many patients renders verbal communication difficult and thus clinical assessment of mental status is often limited. A mild slowly progressive dementia is common. Some clinicians have found dementia in some degree in 60 to 80 per cent of their patients. Jackson et al found the mean I.Q. in 16 consecutive patients to be only slightly below normal. Kimura et al and Fisk et al found that cognitive deficits occurred in subtests requiring visual scanning. Pirozzolo recently found that cognitive impairment correlates with visual rather than overall motor deficit.

The concept of “subcortical dementia” was advanced by Albert et al on the basis of detailed neuropsychological testing in five PSP patients. Its hallmarks were forgetfulness, slowness in execution and difficulty in timing mental tasks resulting in impaired ability to manipulate acquired knowledge. There were no “cortical” deficits such as aphasia, agnosia or apraxia. However, Perkin et al noted dysphasia in two severely demented PSP patients which they ascribed to cortical pathology and they and others have questioned the reality of “subcortical dementia”.

Maher et al and Cambier et al have recently noted that PSP patients do poorly on tests sensitive to frontal lobe dysfunction. Recently, Pillon et al found that PSP patients differed from those with Parkinson’s disease and Alzheimer’s disease in tests of attention, lexical fluency and imitation behavior. Depression and emotional disorders were also most common in patients with PSP. These observations pointing to frontal lobe dysfunction are consistent with the PET scan evidence cited above of frontal hypometabolism. Some of these features - forgetfulness and emotional disorders - are also consistent with temporal lobe dysfunction. We have observed in several of our patients inappropriate and involuntary laughter and hypersexual behavior exacerbated by levodopa therapy which may also reflect temporal lobe pathology.

Pathology

The pathological features initially described by Steele et al have been confirmed by subsequent studies in all the essential...
features. The typical findings are neuronal cell loss associated with gliosis and neurofibrillary tangles (NFT’s) in the subthalamic nucleus, globus pallidus, dentate, substantia nigra, locus ceruleus, periaqueductal gray matter and other brain stem nuclei.

There has been some controversy regarding involvement of the cerebral cortex. It has generally been thought to be spared or minimally affected, although Steele et al had noted somewhat more NFT’s in the cerebral cortex than in control cases in several of their cases. Ishino et al and others have found NFT’s in the cerebral cortex and a pattern of neuronal loss different from that of Alzheimer’s disease in its topography and in its morphology. A predilection for the temporal lobe and especially the hippocampus has been noted. This would seem consistent with the CT and EEG findings, the occurrence of seizures and behavioral disturbances suggestive of temporal lobe dysfunction. Ishino et al argue that there is a specific cortical lesion. The total number of patients studied, however, has been relatively small and may fail to provide an adequate picture of the full range and frequency of cortical involvement.

The anatomical substrate of the oculomotor and eyelid dysfunctions also remains undefined. Although the spinal cord has been studied infrequently and amyotrophy has not been a prominent feature of PSP there has been evidence of spinal motor neuron involvement in several cases including one personally observed case.66

The neurofibrillary tangles (NFT’s) of PSP, chiefly of the globus type (Figure 3) have been thought to be unique to this disease. Ultrastructural studies have shown that they consist of interlacing bundles of straight filaments 15 nm in diameter instead of the paired helical filament (PHF) typical of Alzheimer’s and other degenerative diseases. Of course, the straight filament may represent an early stage in the development of PHF’s. Both share some antigens with microtubule fractions derived from normal brain. However, this study used polyvalent antibody preparations. Consequently, due to the complex protein composition of microtubules, this observation does not permit conclusions regarding the relationships of the two types of NFTs. Further studies with monovalent antibodies are needed to clarify this issue.

**Figure 3 — Neurofibrillary tangles of globus type in nerve cells of the substantia nigra from a personal case of PSP. Bielschowsky silver stain. Photomicrograph courtesy of Douglas Miller M.D.**

### Chemical Pathology

The chemical pathology of PSP has only recently been investigated. Cerebrospinal fluid homovanillic acid, the terminal metabolite of dopamine catabolism, has been low in a number of cases with obvious parkinsonism but normal in one patient with only minor parkinsonism. Presumably the low levels of homovanillic acid reflect the nigral degeneration noted in pathological studies.

Striatal dopamine depletion has been found in the caudate and putamen but not in the nucleus accumbens or the limbic cortex. The depletion in the caudate equaled or exceeded that in the putamen. Thus the pattern of dopamine loss differs from that observed in Parkinson’s disease. The mesolimbic system is involved in the latter and the depletion of dopamine is greater in the putamen than in the caudate. A marked loss of striatal D-2 dopamine receptors has been found in post-mortem studies as well as in the PET scans cited above using labelled bromspiperone as ligand. The loss of dopamine receptor sites in the striatum probably explains the refractoriness of PSP patients to levodopa therapy. A similar loss would be expected in striato-nigral degeneration and perhaps other forms of multiple system atrophy.

Deficiency of cholinergic markers has also been found but is less marked than in Alzheimer’s disease. It was mild in the cerebral cortex, moderate in the putamen (50% loss) but marked in the substantia innominata in several patients studied by Ruberg et al. The loss of striatal cholinergic markers may correlate with the loss of dopamine receptors, both reflecting the loss of striatal neurones. However, brain choline acetyltransferase activity was normal in two severely demented PSP patients studied by Kish et al. The meaning of these variations in data awaits further study but they have led Young to suggest the possibility of using cholinergic agents in the treatment of PSP.

### Treatment

Treatment remains palliative and generally unsatisfactory. The major effect of drug therapy has been partial alleviation of the parkinsonian components to a lesser degree than is ordinarily observed in Parkinson’s disease. It had been noted shortly after the introduction of levodopa therapy that PSP patients responded poorly. With subsequent experience it has become apparent that PSP accounts for a large proportion of l-dopa treatment failures among patients erroneously classified as idiopathic parkinsonism.

Jackson et al recently reviewed published observations on drug treatment in 91 cases. Adding to these a number of observations gleaned from more recent reports yields data on a total of 112 patients. All were treated with levodopa, but only 39 responded, generally for periods of one year or less. Limb rigidity and Bradykinesia responded but axial dystonia and the ophthalmoplegia were not affected. In our experience occasional patients do respond, however, to large doses of levodopa of the order of 500 mg levodopa combined with carbidopa four to six times daily. Psychotoxicity occurs frequently and may preclude a useful benefit. Dopamine receptor agonists have also proved disappointing.

Rafal and Grimm reported that methysergide ameliorated dysphagia, ophthalmoplegia and visually guided behavior as well as parkinson symptoms in a series of 12 patients. Others, however, have encountered limited success with this agent.
In our patients methysergide has not shown any apparent effect. Tricyclic antidepressants have been reported to yield some limited benefit in gait and rigidity and apraxia of eyelid opening. We have found it quite effective in three patients with involuntary laughter. A similar benefit has been described in patients with multiple sclerosis. Anticholinergics and amantadine have been minimally effective in alleviating the parkinsonian features.

Although they cannot alter the course of the disease, physical, speech and occupational therapy may assist the patient and family in coping with gradually progressive motor disabilities. Education of the patient, family and attendants is an important aspect of management. An understanding of these patients' particular disabilities can considerably ameliorate their families' efforts to care for them and help maintain a reasonable quality of life in the advanced stages of the disease. Prisms have not proved effective in managing the diplopia. Indeed, the ocular-motor defects often deprive patients of any benefit from using the ordinary bifocal lenses to which they had been accustomed. Severe dysphagia may require nasogastric tube feeding and eventually feeding gastrostomy or jejunostomy. Good supportive nursing care is required in the terminal stages.

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