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Foreword

We live in a time of rapid change and scientific discovery. In the field of medicine, advances are occurring at such a fast rate that few of us can keep abreast of the developments even in a narrow area of specialization. To meet this challenge, we need to take advantage of all possible means of communication.

The World Federation of Neurology is continuing its efforts to disseminate new knowledge regarding neurological disorders through its World and Regional Congresses, as well as through the publication of the four journals which it sponsors: the *Journal of Neurological Sciences*, *Acta Neuropathologica*, the *Journal of Neuroimmunology*, and the *Journal of Neurovirology*.

The articles included in this volume, which form a short course on important neurological problems, reflect a new effort to make the latest information available to practitioners of neurology. If this course proves useful, it may serve as a model for other special courses to be conducted in other regions or in association with subsequent congresses.

We are indebted to the Congress Organizing Committee and to Dr Theodore Munsat, who have been responsible for organizing these courses and have made it possible for them to be held in association with the 6th Asian and Oceanian Congress of Neurology.

Richard L. Masland, M.D.
President
World Federation of Neurology

Preface

One of the major challenges to today's medical profession is keeping clinical skills up-to-date with a constantly expanding knowledge base. New and clinically useful information is accumulating at an astounding rate and this is certainly more true of neurology than of most other medical disciplines. We are living at a time when our understanding of CNS function and dysfunction has taken a dramatic leap forward and it is quite clear that this is only the beginning. The next decade will undoubtedly bring even greater advances. How does the busy clinician or academician keep abreast of these developments?

Many approaches have been tried with varying degrees of success. These include the traditional avenues of lectures, books and journals as well as conferences, audiotapes, videotapes, slide/audiotape packages, computer-assisted instruction and self-instructional, patient-oriented, problem-solving packages.

Somewhat surprisingly, international congresses have not been used for formal Continuing Medical Education (CME) purposes. Although the content material is certainly educational and presents state-of-the-art information, the organization of the material is not particularly geared for CME goals. In this regard, the 6th Asian and Oceanian Congress of Neurology has taken a leadership position in presenting formal, organized CME as part of the official scientific program.

CME material was presented in a lecture format by acknowledged experts and leaders in that particular field. The course was presented throughout Day 1 of the Congress and at specified times on other days. Thus participants were able both to hear about new scientific advances and also receive more formally organized CME given by an outstanding faculty.

It is this CME program that forms the basis of this volume entitled 'Topics in Contemporary Neurology'. The individual presentations represent both an update and review of a specific topic and will hopefully serve as a valuable educational exercise for those unable to attend the Congress.

The Organizing Committee of the Congress, and in particular Ching-Chang Hung, M.D., Chairman of the Program Committee, are to be highly congratulated for their pioneering and most successful efforts. One hopes that future international congresses will follow their lead and incorporate CME as part of the program.

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Amyotrophic lateral sclerosis

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INTRODUCTION

Recent developments and attitudinal shifts suggest that the amyotrophic lateral sclerosis (ALS) patient and his family are beginning to receive better care. Also, for the first time, the broader scientific community has begun to consider ALS as a disease worthy of serious and intense investigation. This review will be a summary of the present status of the disease, though it will of necessity be selective. Emphasis will be placed on recent developments; the older literature and discounted theories or treatments will be covered only if they elucidate more recent information.

PROBLEMS IN NOSOLOGY

Definitions

In the years following the early descriptions, ALS suffered the nosologic growing pangs of other neurologic diseases. Several other terms such as progressive muscular atrophy, primary lateral sclerosis, progressive bulbar palsy and spinal muscular atrophy were introduced into the literature to describe presumed variants. In addition, 'ALS' patients were described whose motor system disorder was caused by a definable, and at times treatable, underlying pathologic process such as syphilis, diabetes or lead toxicity.

It is quite certain that patients with typical ALS may present with motor involvement confined to the bulbar muscles, progressive bulbar palsy. These patients, who initially have varying degrees of a combination of pseudo- and true bulbar palsy have a poorer prognosis and tend to be older. The disseminated nature of the motor involvement can often be detected by biopsy of clinically normal muscle or with electromyography.

The term primary lateral sclerosis has been used in a somewhat more ambiguous manner. By common usage it refers to patients with progressive upper motor neuron (UMN) signs only but has also been applied to patients with late onset myelopathy, possibly due to a demyelinating process. It is generally accepted that when ALS begins as a pure UMN syndrome it always evolves into a full motor neuron disease within a relatively short period of time. Here too, muscle biopsy and electromyography may reveal evidence of denervation which is not apparent clinically. The neostigmine provocative test[1] can be used to bring out latent fasciculations (the patient is given 1 mg i.m.) The limbs and particularly the tongue are then observed for fasciculations.

The situation with respect to progressive muscular atrophy (PMA) is less clear. A number of patients with progressive lower motor neuron disease and autopsy evidence of ALS have been described. However, appropriate questions have been raised regarding the adequacy of both clinical and pathologic examination in these patients. In a remarkably thorough examination of whether PMA is clinically or pathologically separable from ALS, Norris[2] has concluded that no justification exists for considering PMA a separate entity. In his own extensive personal series only 9% of all motor neuron disease patients had clinical 'PMA' and most of these were still under observation.

The clinical variability of the spinal muscular atrophies (SMA) became established only after the routine use of histochemistry. This new way of looking at muscle pathology quickly resulted in a number of significant alterations in neuromuscular nosology. It became clear that infantile spinal muscular atrophy was not uniformly fatal and that many patients with early onset of disease survived into adult life, at times with only modest functional disability. Large numbers of patients carrying a diagnosis of 'limb-girdle dystrophy' were re-examined in the light of these new findings. It became apparent that as many as 50% of patients carrying this diagnosis in fact had a spinal muscular atrophy. Several characteristics clearly separate SMA from ALS: upper motor neuron signs never develop; the onset of SMA is much earlier than ALS; the vast majority of SMA patients are symptomatic by age 20 while very rarely does an ALS patient develop symptoms before this age; the progression is much more rapid and malignant in ALS; SMA is familial in 50% of patients, while familial incidence is relatively uncommon in ALS in the United States; bulbar involvement is very uncommon in SMA (with the exception of tongue fasciculations) and usual in ALS. Thus, by a number of criteria, ALS and SMA appear to be distinct and separable diseases.

We would suggest a rather rigid definition of the disease, as follows. ALS is a disease confined to the voluntary motor system characterized

by progressive degeneration of 'corticospinal' tracts and α-motoneurons. Although exceptions exist, ALS is defined as much by the absence of other neurologic and organ system involvement as it is by the unique confinement of the degeneration to the voluntary motor system.

EPIDEMIOLOGY

With the exception of the Mariana Islands (Guam) and the Kii Peninsula (Japan), where it is 100 times more common, ALS displays a remarkably constant incidence, prevalence, duration of disease and death rate throughout the world. The epidemiologic literature has been well summarized by Bobowick and Brody[3] and more recently by Kurland.[4] The prevalence rate (number of affected patients per 100,000) is 3.56 in Finland (with possibly a higher level in southeastern counties),[5] 3.0 in Israel,[6] and 6.4 in Lehigh County, Pennsylvania.[7] Incidence rates (number of new patients per 100,000 births) are also quite uniform, with reports of 1.0 and 0.85 in Sweden[4, 8] 1.32 in Lehigh County, Pennsylvania,[7] and 0.64 in Sardinia.[9] Both prevalence and incidence rates tend to be lower in countries with less developed medical systems, for example, Mexico,[10] suggesting that the higher numbers may in fact be more accurate. The world-wide similarity of incidence, prevalence and mortality rates suggests that, if an environmental factor is present, it must be world-wide in distribution.

Kahana et al.[6] in Israel found no change in incidence during the period 1960-1970. The incidence of both ALS and multiple sclerosis (MS) in immigrant groups in England was studied by Dean et al.[11] No differences were observed in any ethnic group.

It has been reported that several other risk factors occur in association with ALS more frequently than expected.[12] There is a positive correlation of disease with exposure to lead and mercury, participation in athletic activities and consumption of at least one quart of milk per day. The statistical techniques used in this study have been criticized.[13]

During the Second World War, 12,601 United States residents worked on Guam for one year or more. In a follow-up study of these individuals, information was available on 10,049. No increased incidence of ALS was observed.[14]

ETIOLOGY AND PATHOGENESIS

Aging

ALS is a disease uniquely limited to adults. Most epidemiologic studies have found a mean age of onset in the range of 52-58 years. In the early 1900s Gowers[15] proposed that certain progressive neurologic disorders, particularly the spinocerebellar degenerations, may be caused by premature aging or 'abiotrophy'. The loss of vulnerable motor cells might then lead to excessive metabolic demand upon remaining motoneurons and eventually result in their premature loss as well. It has been demonstrated by physiological[16] and anatomical[17] techniques that significant motor unit drop-out begins after age 55 and continues until death. This mechanism, possibly compounded by a genetic or environmental factor, could lead to a clinical picture such as ALS.

Toxins

Environmental toxins

The observation that exposure to environmental lead can cause prominent motor deficit simulating ALS[18] has led to the suggestion that lead toxicity may be causative in at least some patients with ALS. It has been reported that a history of exposure to lead is more common in ALS patients than other disease controls and that spinal cords of ALS patients have a 25-fold increase in lead content.[19] Others have reported normal lead levels in ALS spinal cords.[20] More recently, Conradi et al.[21-23] have again raised the question of lead levels in ALS. They were not able to demonstrate abnormal protein binding, but did observe significantly elevated plasma levels in 16 ALS patients and elevated cerebrospinal fluid (CSF) levels in 12.

The inordinately high incidence of ALS on Guam and on the Kii Peninsula of Japan, with which it shares common environmental features, has led Yase[24] to study soil and other environmental minerals in the area. A suggestive relationship to high manganese levels is being evaluated further.

Kilness and Hichberg[25] reported four cases of sporadic ALS, with typical clinical manifestations, from a sparsely settled area in western South Dakota. These patients all lived within 15 km of each other. The authors pointed out that this same area was endemic for farm animal selenium intoxication because of the high natural soil content. Twenty patients with ALS, including one from the 'endemic' area, were subsequently evaluated by Norris and U[26] for urinary selenium excre-

tion with atomic absorption spectrometry. They were unable to confirm this hypothesis.

Endogenous toxins

In 1973, Wolfgram and Myers[27] reported that sera from patients with ALS were toxic to mouse anterior horn cells in tissue culture. This report has triggered a number of subsequent studies, some confirmatory[28, 29] but others not so.[30, 31]

Viral agents

The suggestion that ALS is the result of the action of a slow virus is an attractive hypothesis and, indeed, is the hypothesis which has received the greatest amount of attention.

Oshiro et al.[32] reported 20-24 nm virus-like crystalline arrays in the muscle, but not the central nervous system, of a single patient with ALS. Tubular structures of 80-85 nm were observed in the rough endoplasmic reticulum of anterior horn cells and cells of the precentral gyrus in a 57-year-old ALS patient.[33]

In 23 ALS patients Kascsak et al.[34] were unable to demonstrate reactivity to a battery of 78 complement fixation and 15 hemagglutination arbovirus antigens. Cremer et al.[35] observed no increase in antibody titers to coxsackie A9 and B 1-6 in 48 ALS patients as compared to 47 matched controls. No increase of neutralizing antibodies to polio or mumps virus was observed in 17 patients studied by Lehrich et al.[36] or 11 patients studied by Jokelainen et al.[37] Although Weiner et al.[38] demonstrated an increase of cold-reactive lymphocytotoxic antibodies in MS and subacute sclerosing panencephalitis (SSPE), no increase was observed in ALS. Cremer et al.[39] found no evidence of antibody rise (15 viruses) in 34 patients.

Cellular immunity in Guamanian ALS was recently studied in detail by Hoffman et al.[40] Guamanian ALS patients were compared with Guamanians with other neurological diseases, normal Guamanians and non-Guamanians with ALS. Only the Guamanian ALS patients showed a decreased response to skin-test antigens, leukopenia and diminished relative and total T cell population. Nine sporadic ALS patients were studied in detail by Behan et al.[41] Three showed cutaneous anergy for streptokinase/streptodornase, polio and *Candida*. All nine showed an impaired T cell response to stimulation by phytohemagglutinin.

Jejunal immune complex deposition in ALS has been reported by researchers in New York[42, 43] and Glasgow.[41] All of seven patients with ALS showed immune complex deposition by immunofluorescence.[43]

In four cases jejunal poliovirus antigen was detected and in one herpesvirus antigen. In two autopsied cases the changes were observed to be most prominent in the proximal jejunum. Only two of 35 control patients showed similar changes.

Five of seven ALS patients examined by Behan et al.[41] showed evidence of polio antigen in the lamina propria, villi and crypts. No deposition was observed in blood vessels. Electron microscopic study of all jejunal biopsy specimens was negative for virus.

Direct immunofluorescence studies revealed moderate amounts of both IgG and C3 along the glomerular basement membrane and mesangia in nine of 33 patients.[44] The patients with renal immune complexes had a more rapidly progressive course. Ten of 23 patients also had demonstrable serum immune complexes. An unsuccessful search for immune complexes in the skin and kidney of seven ALS patients was recently reported by Palo et al.[45] Surveys of histocompatibility antigens in ALS have revealed contradictory results which cast doubts on the significance of these observations. Attempts to culture a transmissible agent have been uniformly unsuccessful.

Gastrointestinal absorption

Animal studies have suggested that gastrectomy may lead to degeneration of anterior horn cells.[46-48] Over the years passing references have been made to gastrointestinal dysfunction in ALS. However, these reports are not well-documented and contain only anecdotal clinical experiences. More organized inquiry into this question[49] has failed to reveal a relationship.

Neurotransmitters

It is not unreasonable to suspect that ALS might be associated with defective neurotransmitter function. The disease is uniquely limited to one neurologic 'system'. There are a number of clinical situations in which parkinsonism and ALS occur in the same patient or the same family, such as Guamanian parkinsonism-motor neuron disease, the Shy-Drager syndrome and viral encephalitis. Relatively few studies, however, have explored this possibility. Brody et al.[50] observed a significant reduction in CSF homovanillic acid (HVA) (the end-product of dopamine catabolism) in seven Guamanian patients with Parkinson-dementia complex. Six Guamanian and five sporadic American ALS patients had a similar reduction but of lesser magnitude. These initial studies were confirmed and expanded by Mendell et al.[51] Both resting levels and the rate of probenecid-induced accumulation of HVA were

found to be depressed in 21 ALS patients. However, no difference in steady-state 5-hydroxyindolacetic acid levels were observed and none of 10 patients showed a therapeutic response to L-dopa. Brait et al.[52] observed a decrease in the striatal monamines dopamine, norepinephrine and serotonin in a single patient with familial parkinsonism and motor neuron disease but also failed to observe a therapeutic response to L-dopa. These authors reported three other sporadic American cases with parkinsonism and motor neuron disease.

Glycine, an inhibitory spinal cord neurotransmitter, was measured in grey and white matter at thoracic, cervical and lumbar levels in four ALS spinal cords.[53] No difference from normal controls was observed.

More recently Engel et al. have reported that CSF levels of thyrotropin releasing hormone (TRH) are depressed in ALS patients[54] and that short-lasting clinical benefit occurs with high-dose intravenous TRH.[55]

Miscellaneous

Cyclic nucleotide metabolism has been studied by Brooks et al.[56, 57] In 37 patients with various forms of motor neuron disease they observed normal plasma levels of cAMP and cGMP but a significant decrease in CSF cAMP as compared to age-matched controls. Although treatment with a phosphodiesterase inhibitor increased CSF levels of the nucleotides, no clinical improvement occurred (Brooks, B.R., personal communication). Cyclic GMP, but not AMP, was reduced in the spinal cord and cerebellum of the wobbler mouse – a proposed animal model of ALS.[58]

Other

Mann and Yates[59] have proposed an abnormality of tRNA synthesis resulting from defective DNA in ALS anterior horn cells. The occurrence of ALS in both of dizygotic twins has suggested a prenatal influence.[60] An abnormality of protein metabolism is suggested by ultrastructural studies of Bunina bodies seen in the anterior horn cells of ALS patients.[61]

THERAPY

Specific pharmacologic agents

Antiviral

The hypothesis that ALS is a result of, or associated with, a slow virus infection of the central nervous system (CNS) has understandably led to trials of putative antiviral agents. In a preliminary report Norris[62] treated 84 patients for six months with guanidine hydrochloride and observed that 30 'seemed to stabilize neurologically, and some even improved'. The complete report, which appeared the following year,[63] observed a lower mortality at six months in those patients treated with a dose of 25 mg/kg/day as compared to a matched patient group treated with 1.5-2.5 mg/kg/day. However, others have not been able to confirm these results.[64]

Therapeutic failures have been reported for isoprinosine in Guamanian ALS[65] and non-Guamanian sporadic ALS;[66, 67] they have also been reported for idoxuridine.[68] Preliminary results with intrathecal interferon are not encouraging (Munsat, T.L., personal observations).

Antispasticity drugs

The history of antispasticity drugs in ALS, as well as other neurologic disorders with UMN deficit, is patchy at the very best. Certain agents, of more recent vintage, deserve comment, however. Diazepam can be of benefit to certain patients, though whether the benefit relates to its CNS psychopharmacologic action or to more specific motor inhibition is unclear. Most patients, however, do not experience significant benefit from diazepam unless the dosage is raised to soporific levels.

Baclofen, a γ-aminobutyric acid derivative, has recently been released for use in the United States. It is particularly effective when the spasticity is of spinal cord origin and is considerably less effective in UMN deficit of cerebral origin such as stroke. Our own experience with ALS patients has been quite gratifying. Most patients with UMN deficit will show functional improvement in gait and less so in upper extremity skills at relatively low doses such as 5 mg t.i.d. Dysarthria and dysphagia due to UMN deficit may also improve. Unfortunately, as the disease progresses higher doses are required for diminishing clinical benefit.

Prominent sialorrhea can be an early and at times very disturbing symptom in patients with bulbar involvement. Artane, amitriptyline and atropine can be of benefit. Occasional patients will have a myasthenic component to their weakness; these rare individuals may show a

temporary response to pyridostigmine or neostigmine. Disturbing cramps, which may be a problem in the early stages of ALS, may respond to membrane stabilizers such as phenytoin and/or carbamazepine.

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