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Dementia of frontal lobe type and amyotrophy

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Dementia of frontal lobe type may precede motor signs in a number of adult patients with amyotrophy. Neuropathological studies have shown neuron loss, spongiosis and gliosis mainly in layers II and III of the frontal and temporal lobes, together with myelin pallor of the subcortical white matter. Golgi studies revealed loss of dendritic spines on the apical dendrite of layer III pyramidal neurons, decreased numbers of dendrites, amputation and tortuosities of dendrites, and distal and proximal dendritic swellings and enlargements. Calbindin D-28K immunocytochemistry revealed a marked decrease in the number of cortical immunoreactive neurons and loss of immunoreactivity in dendrites of the remaining cells. These features indicate that pyramidal and non-pyramidal neurons in layers II and III are severely damaged, and suggest that cortical processing is seriously impaired in patients with frontal lobe type dementia.

Keywords: Amyotrophy – Calbindin – Calcium binding protein – Cerebral cortex – Cortical processing – Dementia – Frontal lobe – Golgi method – Motor neuron disease

INTRODUCTION

Motor neuron disease associated with dementia and Parkinsonism is common in distinct populations of the Mariana Islands, New Guinea and the Kii Peninsula of Honshu Island. Patients have, together with classical signs of amyotrophic lateral sclerosis (ALS), large numbers of neurofibrillary tangles in the cerebral neocortex, hippocampus, amygdaloid complex, substantia innominata, hypothalamic nuclei, locus niger, locus ceruleus, reticular formation, dorsal nucleus of the vagus and other nuclei of the brainstem. Senile plaques are absent (Hirano, 1973; Garruto and Yase, 1986; Kurland, 1988). Sporadic and familiar cases with similar characteristics have been, however, rarely observed in Western countries (Hirano *et al.*, 1967; Nelson and Prensky, 1972; Forno and O'Flanagan, 1973; Meyers *et al.*, 1974; Mata *et al.*, 1983; Schmitt *et al.*, 1984).

Motor neuron disease associated with dementia can also occur in Alzheimer's disease, Pick's disease, Shy-Drager syndrome, olivopontocerebellar atrophy and other degenerative diseases (Hudson, 1981). Until now, only one patient has been described with motor neuron disease, Parkinsonism and dementia, in which the neuropathological examination revealed classical ALS together with Alzheimer-type changes in the brain and diffuse Lewy body-like intracytoplasmic inclusions (Delisle *et al.*, 1987). It must be noted, however, that inclusion bodies in the brainstem and cerebral cortex are probably more common than previously suspected in a number of patients with motor neuron disease (Lowe *et al.*, 1989).

Another group of patients suffer from dementia with predominant frontal signs and amyotrophy. In addition to lower motor neuron loss, the main neuropathological findings are nerve cell loss, spongiosis and gliosis in layers II and III of the frontal (and temporal) cortex, and subcortical myelin pallor and gliosis. First described in the thirties (Ziegler, 1930; Wechsler and Davidson, 1932; Uematsu, 1935), further cases of dementia and ALS were reported from France (Michaux *et al.*, 1955; Delay *et al.*, 1959) and Japan (Furukawa, 1959). Although the association of dementia and amyotrophy has raised much concern in Japan (see Yuasa, 1970; Nagano *et al.*, 1977; Mitsuyama and Takamiya, 1979; Ando and Miyakawa, 1982; Mitsuyama, 1984; Morita and Ikeda, 1986; Morita *et al.*, 1987), the disease is distributed world-wide (Myrianthopoulos and Smith, 1962; Brownell *et al.*, 1970; Hudson, 1981; Wikstrom *et al.*, 1982; Horoupian *et al.*, 1984; Gilbert *et al.*, 1988; Neary *et al.*, 1988; Ferrer *et al.*, 1991a, 1992c).

In this study we have focused our attention on the abnormalities in the cerebral cortex in patients with frontal lobe type dementia and amyotrophy in an attempt to learn the morphological substrates of this type of dementia.

The neurological abnormalities and neuropathological findings in four patients with frontal lobe type dementia and motor neuron disease, who were personally examined, are the main subjects of the present work (Table I). In addition to current neuropathological methods, the short interval between death and tissue processing has permitted, in two cases (cases 1 and 2, Table I), the application of the rapid Golgi method, and calbindin D-28K and parvalbumin immunocytochemistry in the study of the cerebral cortex.

TABLE I. Patients suffering from dementia of frontal lobe type and amyotrophy

Case	Age at onset	Gender	First symptoms	Motor signs (m)	Course (m)	Tissue processing (h)
1	37	F	Mental	16	20	5
2	69	F	Mental	13	23	2
3	67	M	Mental	13	18	>12
4	52	M	Mental	6	16	<3

F, feminine; M, masculine; m, months; h, hours.

Although the delay between death and tissue processing produces poor impregnations and artifacts which preclude any interpretation (Williams *et al.*, 1973; Buell, 1982; de Ruiter, 1983), the Golgi method is particularly useful to learn the modifications of individual neurons when used in optimal conditions (Braak and Braak, 1985).

Calbindin D-28K and parvalbumin are calcium-binding proteins which in the cerebral cortex and hippocampus are found in different populations of local-circuit neurons which use gamma-aminobutyric acid (GABA) as a neurotransmitter (Celio, 1986, 1990; Kosaka *et al.*, 1987, 1989, 1990; Hendry *et al.*, 1989; Kosaka and Heizmann, 1989; Demeulemeester *et al.*, 1988, 1989, 1991; van Bredererode *et al.*, 1990). The use of calbindin D-28K and parvalbumin immunocytochemistry in free-floating sections of the frontal cortex has been an enlightening procedure to discover the morphology of different types of non-pyramidal neurons.

Details of these methods are given elsewhere (Ferrer *et al.*, 1991a, 1992c).

CLINICAL SIGNS

The age at onset was wide-ranging, from 38 to 71 years, but the clinical course was short in every case, between 1 and 2 years from the beginning of the symptoms to death (Table I).

Changes in personality and mood, and declining mental capabilities preceded the appearance of motor signs by 1 year. Mental abnormalities included apathy, difficulty in formulating and carrying out new plans, loss of attention and loss of short-term memory, language impoverishment, decreased activity and loss of general awareness. The neurological examination revealed grasping, positive jaw and snout reflex and repetitive acts. These clinical symptoms and signs are characteristic of prefrontal lobe syndromes (Fuster, 1989).

Motor signs included difficulties in swallowing, fasciculations of the tongue, amyotrophy of the hands, loss of muscular strength and generalized fasciculations. Pyramidal signs (including a Babinski sign) occurred in two patients (cases 2 and 3, Table I). Slight rigidity was present in one case (case 2, Table I).

Similar neurological findings have been described in other patients with dementia of frontal lobe type and amyotrophy (references, see above). According to these reports, most patients start with mental symptoms, but motor signs at onset may occur in a small number of cases. Lower motor signs predominate in most patients, whereas increased tendon reflexes and a Babinski sign are found in only about 25% of the patients. Slight extrapyramidal signs are found in approximately 25% of cases.

CT scans of the brain reveal atrophy of the frontal (and temporal) lobes. RNM studies show, in addition to cortical atrophy, bilateral lucencies in the subcortical and periventricular white matter. The EEG is almost normal.

GENERAL MORPHOLOGICAL FINDINGS

The frontal lobes were atrophic in our four cases with dementia of frontal lobe type and amyotrophy (Fig. 1A); the temporal lobe was atrophic in three cases. The main morphological alterations, as seen in paraffin sections, were loss of neurons, status spongiosus (coarse vacuolization of the neuropil) and gliosis in layers II and III of the frontal lobes, and to a lesser extent of the temporal lobes as well as (Fig. 1B). A moderate gliosis was also observed in the inner cortical layers. The cerebral white matter of the frontal lobes had diffuse myelin pallor and slight gliosis in every case. Neurons in the white matter of the frontal lobes were preserved.

Very small numbers of senile plaques and neurofibrillary tangles were present only in one case (case 2, Table I), and were absent in the remaining. One man, aged 48, with dementia, Parkinsonism and motor neuron disease who had large numbers of neurofibrillary tangles in the neocortex, hippocampus, locus ceruleus, substantia nigra and other nuclei of the brainstem, was not included in the present series. Pick bodies and Lewy bodies were absent in every case.

The thalamus, and the caudate and putamen, showed mild neuron loss and gliosis (cases 2, 3 and 4, Table I). Slight neuron loss occurred in the pallidum and subthalamus in one case (case 2, Table I). The claustrum and amygdaloid complex were normal. The different nuclei of the rostral forebrain and septal region were unremarkable. Decreased numbers of neurons, mild gliosis and spongio-

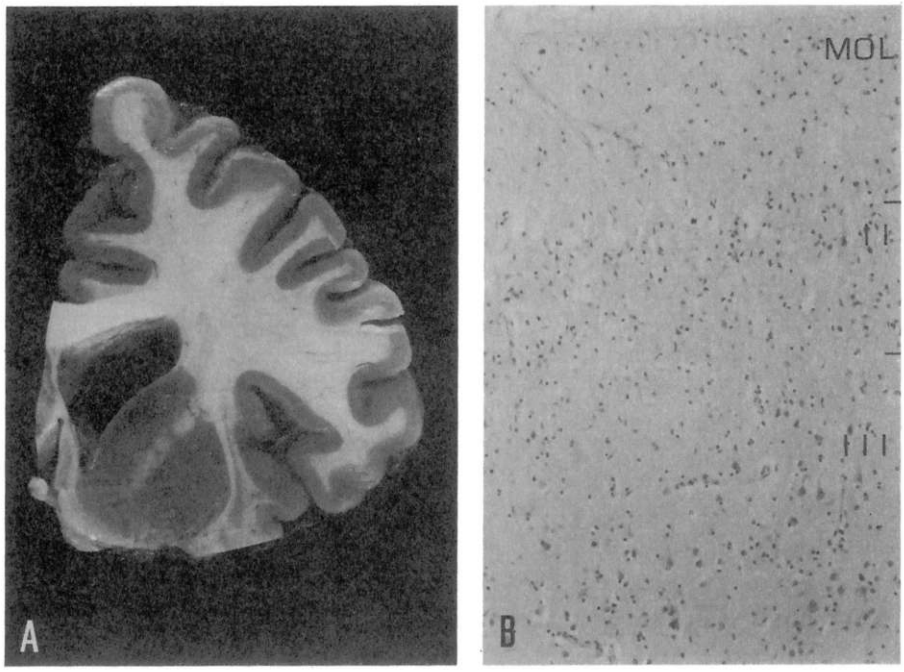

FIG. 1. (A) Frontal atrophy in a patient with dementia of frontal lobe type and amyotrophy (case 4). (B) Neuron loss, gliosis and spongiosis in layers II and III of the frontal cortex (case 2). Mol: molecular layer. H&E × 112.

sis, and pigment granules in the neuropil were found in the locus niger in two patients (cases 2 and 3, Table I).

The cerebellum, including the dentate nuclei, as well as the pontine nuclei and the olivary complex, was normal.

Moderate neuron loss and gliosis occurred in the motor nuclei of the medulla oblongata and spinal anterior horn. Scarce chromatolytic neurons were encountered, but axonal swellings filled with phosphorilated neurofilaments (Hirano *et al.*, 1984; Muñoz *et al.*, 1988; Leigh *et al.*, 1989), although common in ALS patients with rapid clinical course, were rare in our patients with dementia and amyotrophy. Eosinophilic intracytoplasmic hyaline inclusions (including Bunina and Lewy-like bodies) in anterior horn cells of the spinal cord were observed in one patient (case 2, Table I). Moderate myelin pallor was found in the bulbar pyramids and pyramidal tracts of the spinal cord in three cases (cases 1, 2 and 3, Table I).

These findings, together with those reported in other patients, stress the idea that frontal lobe type dementia and amyotrophy is a multisystematic atrophy. Involvement of the frontal and temporal neocortex, and lower motor neurons of the medulla oblongata and spinal cord, are constant features, but the caudate and putamen, thalamus, locus niger and pyramidal tracts may be affected in a number of cases as well.

STUDIES WITH THE GOLGI METHOD

A few Golgi studies have been carried out in the nervous tissue of patients with ALS. One study described the morphologic abnormalities observed in the large anterior horn cells (Kato *et al.*, 1987), while others reported reduced numbers of dendrites, dendritic swellings and distortion in Betz cells of the primary motor cortex (Hammer *et al.*, 1979; Udaka *et al.*, 1986; Pugh and Rossi, 1991). Other studies were focused on the cerebral cortex in patients with dementia associated with ALS or with amyotrophy (Horoupian *et al.*, 1984; Ferrer *et al.*, 1991a), including one woman affected by the Klüver-Bucy syndrome related to changes in the medial temporal lobe which was combined with characteristic abnormalities in the frontal lobes (Dickson *et al.*, 1986). In patients with frontal lobe type dementia and amyotrophy, anomalies occurred in pyramidal and non-pyramidal neurons located in layers II and III of the frontal and temporal cortex, but the occipital (primary visual) and parietal (primary and associative somatosensory) lobes were preserved in the two cases personally examined with the Golgi method (cases 1 and 2, Table I). Several small and medium-sized pyramidal neurons in the upper cortical layers displayed reduced dendritic arbors and marked reduction in the number of dendritic spines, together with proximal dendritic swellings and tortuosities and amputations of basilar and collateral dendrites (Fig. 2). Non-pyramidal neurons in the uppers layers also showed reduced dendritic arbors and mutilation of dendrites. In contrast with these findings, neurons in layers IV, V and VI were preserved.

These morphological abnormalities in cortical neurons

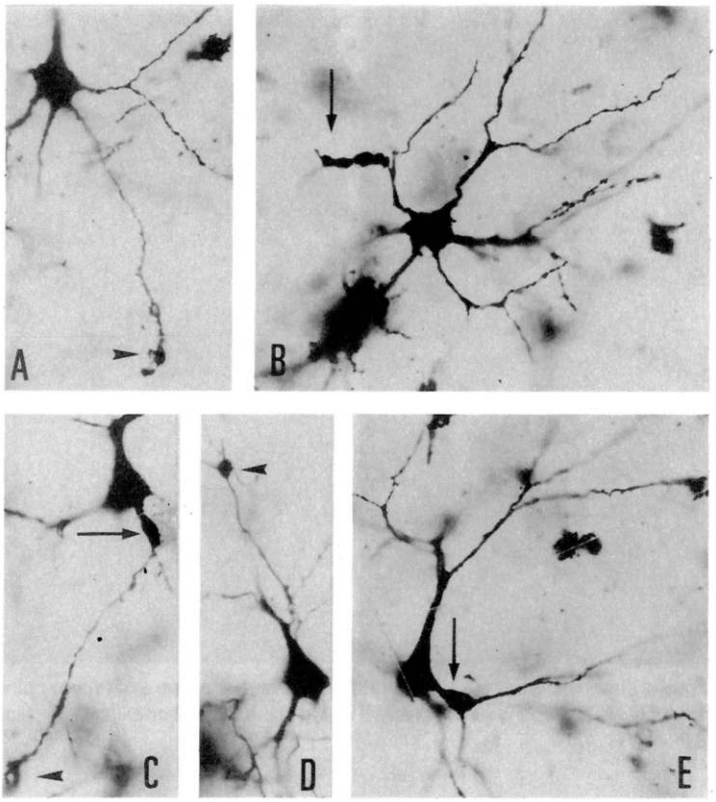

FIG. 2. Golgi impregnated neurons in layers II and III of the frontal cortex in patients with dementia of frontal lobe type and amyotrophy (cases 1 and 2). Decreased numbers of dendrites and loss of dendritic spines, together with tortuosities and amputations of dendrites, are common features. Distal dendritic swellings (A, C and D) (short arrows), and distal (B) and proximal (C and E) dendritic enlargements (long arrows) are also encountered in some neurons. Rapid Golgi method × 280.

are not specific, since similar observations have been made in the cerebral cortex or patients with Alzheimer's disease, Pick's disease and spongiform encephalopathies (Scheibel, 1979; Landis *et al.*, 1981; Wechsler *et al.*, 1982; Ferrer *et al.*, 1981, 1990b), and in experimental Creutzfeldt-Jakob disease (Hogan *et al.*, 1987; Kim and Manuelidis, 1989).

Abnormalities were seen neither in normal cases, nor in the prefrontal cortex of patients with classic ALS non-associated with dementia. Therefore, the observed alterations are artifacts of delayed fixation but rather images of actual degenerating cells (Ferrer *et al.*, 1991a). Focal dendritic outgrowths, as seen in pyramidal and non-pyramidal neurons in patients with Alzheimer's disease (Scheibel and Tomiyasu, 1978; Probst *et al.*, 1983; Ferrer *et al.*, 1983, 1990b), were not found in patients with frontal lobe type dementia and motor neuron disease.

Quantitative studies have shown significant decreased numbers of dendritic spines on the apical dendrite of layer III pyramidal cells in the frontal cortex (left area 8, crown region) of patients with frontal lobe type dementia and amyotrophy (cases 1 and 2, Table I), when compared with non-demented ALS cases (aged 58, 62, 65 and 56 years) and to age-matched controls ($n = 8$, age 57 ± 12.2 years). Dendritic spines were counted on the 500-μ-long proximal segment of the apical dendrite of layer III pyramidal neurons and the results were expressed as the mean values ± S.D. obtained from the measurement of 15 neurons in every case. Patients with dementia and motor neuron disease had significantly (Mann-Whitney U-test, $p < 0.01$) fewer numbers of dendritic spines (236 ± 28) than non-demented ALS cases (353 ± 41) and age-matched controls (368 ± 36).

Reduction in the number of dendritic spines has also been observed in pyramidal cells of the cerebral cortex and hippocampus in patients with Alzheimer's disease, spongiform encephalopathy (Creutfeldt-Jakob disease), Pick's disease, dementia paralytica and chronic alcoholism (Mehraein *et al.*, 1975; Buell and Coleman, 1979, 1981; Flood *et al.*, 1987; Ferrer *et al.*, 1986; de Ruiter and Uylings, 1987; Catalá *et al.*, 1988; Ferrer and Gullotta, 1990). Focal overproduction of spines, as seen in patients with

Alzheimer's disease (Scheibel and Tomiyasu, 1978; Ferrer *et al.*, 1983), was not seen in patients with frontal lobe type dementia.

CALBINDIN D-28K AND PARVALBUMIN IMMUNOCYTOCHEMISTRY

Calbindin D-28K-immunoreactive neurons in the normal frontal cortex are small multipolar and bitufted cells in layers II and III, bipolar and double-bouquet neurons in layer III, and multipolar neurons in layers V and VI. The vast majority of calbindin D-28K-immunoreactive cells are found in the upper cortical layers (Hendry *et al.*, 1989; Demeulemeester *et al.*, 1988, 1989, 1991; DeFelipe *et al.*, 1989a, 1990; van Brederode *et al.*, 1991; Ferrer *et al.*, 1992c). Calbindin-immunoreactive neurons in patients with frontal lobe type dementia and amyotrophy were decreased in number, and the remaining cells had reduced immunoreactive dendritic arbors (Fig. 3). Quantitative studies revealed that these reductions are significant when compared with similar counts in age-matched controls (Ferrer *et al.*, 1992b).

Parvalbumin-immunoreactive cells in the normal frontal cortex are similar to basket neurons and chandelier cells previously described in the neocortex and hippocampus (Hendry *et al.*, 1989; DeFelipe *et al.*, 1989b; Blümcke *et al.*, 1990; Lewis and Lund, 1990; Nitsch *et al.*, 1990; Soriano *et al.*, 1990; van Brederode *et al.*, 1991). Parvalbumin-immunoreactive cells in the neocortex are found in all cortical layers, except the molecular layer, and predominate in layers IV and V. Parvalbumin-immunoreactive neurons were preserved in the cerebral cortex of patients with dementia of frontal lobe type and amyotrophy (Ferrer *et al.*, 1992b).

A similar decrease in the number of calbindin D-28K-immunoreactive cells, together with a preservation of parvalbumin-immunoreactive neurons is found in the neocortex of most patients with Alzheimer's disease (Ichimiya *et al.*, 1989; Hof *et al.*, 1991; Ferrer *et al.*, 1991c, 1992d). However, parvalbumin immunoreactivity is decreased in patients with very advanced Alzheimer's disease (Arai *et al.*, 1987; Satoh *et al.*, 1991; Ferrer *et al.*, 1991c).

Based on these findings, it can be suggested that parvalbumin-immunoreactive cells are more resistant than calbindin D-28K-immunoreactive cells in different degenerative diseases, a feature which correlates with the observation that parvalbumin-immunoreactive cells are resistant to epileptic seizures and to cerebral ischemia (Kamphuis and Lopes da Silva, 1990; Nitsch *et al.*, 1989). Nevertheless, since neuron loss predominates in the upper cortical layers in patients with frontal lobe type dementia, the preservation of parvalbumin-immunoreactive cells in

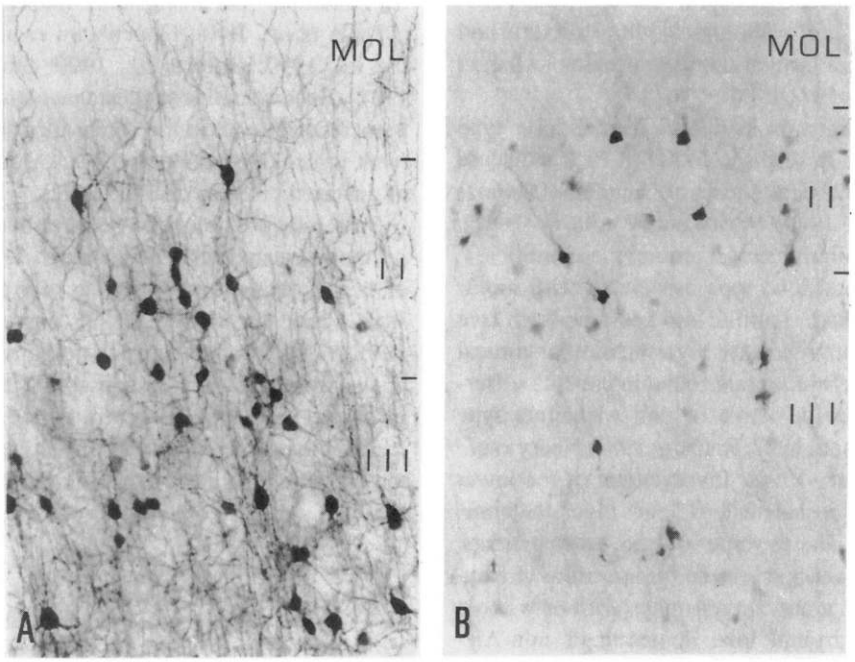

FIG. 3. Calbindin D28K-immunoreactive neurons in the frontal cortex (left area 8, crown) in a control case aged 72 (A) and in one patient with dementia of frontal lobe type and amyotrophy (case 2) (B). Decreased numbers of neurons and reduced dendritic arbors in the remaining cells are found in the patient with dementia. Mol: molecular layer. × 112. Paraformaldehyde fixation (24 h), 50 μ thick cryostat sections processed free-floating following the avidin-biotin method. Calbindin D-28K monoclon a1 antibody (Sigma, clone CL-300 purified from chicken gut) used at a dilution of 1:800.

these patients can be a mere consequence of their deeper position in the cerebral cortex.

DESTRUCTION OF THE UPPER CORTICAL LAYERS AS A CAUSE OF DEMENTIA

The present results indicate that pyramidal and non-pyramidal neurons in layers II and III of the frontal and temporal cortex are severely damaged in patients with frontal lobe type dementia. These abnormalities probably impair normal cortical operations (Eccles, 1984) because of the involvement of local-circuit neurons and projection cells. These latter neurons project to, and receive projections from, other cortical regions (Jones, 1984). In summary, our morphological data suggest that destruction of cortico-cortical connections and intracortical circuits in the frontal (and temporal) cortex is probably the cause of the mental impairment in patients with frontal lobe type dementia.

A THEORY OF PATHOGENIC MECHANISMS

Neuron loss, gliosis and vacuolization of the neuropil are found in spongiform encephalopathies. However, the characteristic "spongiform change" typical of Creutzfeldt-Jakob disease (Masters and Gajdusek, 1982) is not found in patients with frontal lobe type dementia and classic motor neuron disease. It must be noted nevertheless, that an amyotrophic form of Creutzfeldt-Jakob disease probably exists on the basis of pathological, ultrastructural and transmission data in a limited number of cases (Allen *et al.*, 1971; Connolly *et al.*, 1988).

Pathological findings in patients' frontal lobe type dementia also differ from those found in Pick's disease and progressive subcortical gliosis of Neumann (Muñoz-García and Ludwin, 1984; Verity and Wechsler, 1987), although certain similarities exist among these entities.

Dementia of frontal lobe type associated with motor neuron disease occurs in familial and sporadic form (see Hudson, 1981 for comprehensive review). Similar clinical and neuropathologic findings are found in patients suffering from frontal lobe dementia of non-Alzheimer type (Brun, 1987; Gustafson, 1987; Risberg, 1987; Neary *et al.*, 1988; Knopman *et al.*, 1990). Involvement of the lower motorneurons, hypoglossal nucleus, locus niger, thalamus and striatum also occurs in some of these latter patients, thus suggesting an overlap between the spectrum of frontal lobe type dementia and amyotrophy (with or without Parkinsonism) and frontal lobe dementia of non-Alzheimer type (with or without Parkinsonism and amyotrophy) (Ferrer *et al.*, 1991a).

We do not know why neuron loss predominates in the upper cortical layers of the cerebral cortex in patients with frontal lobe type dementia, but it is of interest that cortical cell death during normal development mainly occurs in two compartments: one is the cortical subplate, the other is the upper level of the cortical plate (see Shatz *et al.*, 1988; Ferrer *et al.*, 1992a for review). The cortical subplate is a transitory structure during development which is composed of neurons that probably serve as targets for thalamic afferents until migrating neuroblasts reach their final positions in the cerebral cortex and definitive thalamocortical connections can be established. Developmental cell death in the cerebral cortex is found in layers II and III in rodents and kittens (Finlay and Slattery, 1983; Pearlman, 1985; Ferrer *et al.*, 1989, 1990a). Naturally occurring cell death in layers II and III is poorly understood, although it probably adjusts the final number of cortical neurons with the number of their targets (Ferrer *et al.*, 1991b; Windrem and Finlay, 1991).

Several theories have been proposed to explain the mechanisms controlling naturally occurring cell death, and it is feasible that different factors are involved in different forms and stages of cell death during development (Oppenheim, 1991). For example, programmed cell deaths in the nematode *Caenorhabditis elegans* are the result of the activation of different genes which may encode different proteins involved in cell killing and engulfment (Hedgecock *et al.*, 1983; Chalfie and Wolinsky, 1990; Avery and Horvitz, 1991; Ellis *et al.*, 1991; Driscoll and Chalfie, 1992). Activation of different proteins also occurs in the nervous system of vertebrates during naturally occurring and induced neuronal death (Martin *et al.*, 1988; Oppenheim *et al.*, 1990; Scott and Davies, 1990; Goto *et al.*, 1990; Shigeno *et al.*, 1990, 1991). Recent studies suggest that naturally occurring and induced cell death in the cerebral cortex during development is also dependent on the activation or the inhibition of different proteins (Ferrer, 1992).

Searching possible links between neuronal death during development and nerve cell death in degenerative diseases of the central nervous system has been the subject of recent studies (see for example Ciba Foundation Symposium 126). Along this line, and according to the data described above, there is the exciting possibility that nerve cell death in frontal lobe type dementia with amyotrophy, and in frontal lobe dementia of non-Alzheimer type, results from the activation of killing genes which remain dormant from the early stages of cortical development.

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