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Epilepsy and neurodegenerative diseases in adults: a clinical review

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ABSTRACT – Neurodegenerative disorders in adults are progressively recognized as one of the major causes of epilepsy. Improved health care, resulting in increased longevity, will unavoidably lead to an increase of epilepsy cases in the elderly. For example, in Alzheimer's disease, almost 10% of the patients present with seizures, eventually necessitating an antiepileptic treatment. We review available data on epidemiology, diagnosis and treatment of the epilepsies when associated with major neurodegenerative disorders. Controlled, prospective studies are lacking.

Keywords: neurodegenerative disorders, dementia, Alzheimer, epilepsy

Neurodegenerative disorders are characterized by selective neuronal loss, with gradual onset and chronic evolution, resulting in a progressive functional deterioration. Although better knowledge of the pathogenesis of these disorders makes it possible to formulate new definitions based on their molecular origins (Williams, 2002), in the absence of reliable biological markers, most diagnoses are based on clinical data, and sometimes radiological data, after ruling out possible metabolic, toxic or infectious etiologies. Selectivity in neuronal loss explains clinical diversity, which may include motor, cognitive symptoms or both.

Neurodegenerative disorders affect two distinct population groups: children, young adults; and the elderly. In the former group, diseases are mostly an expression of a genetic defect and will not be discussed in this article. However, in the elderly they are much more frequent (Alzheimer's disease, Parkinson, other dementias...), mainly influenced by environmental factors and to a lesser extent by genetic factors. Given that age is the major risk factor in these pathologies, and given the continuous aging of the population in Western countries, physicians in their practice will be more and more confronted to these pathologies, with their associated co-morbidities. In this context, epilepsy raises complex diagnostic and therapeutic problems, which will be discussed below. At this point, it is important to differentiate seizures related to the neurodegenerative disorder from symptomatic seizures secondary to an underlying metabolic or infectious cause frequently encountered in this age group. Although the distinction is not always clear, the discussion which follows only concerns epilepsy, defined as a disorder characterized by the repetition of unprovoked seizures.

Epilepsy in the elderly: the role of neurodegenerative etiology

Age is an independent risk factor both for neurodegenerative diseases (Van Duijn, 1996, McCullagh *et al.*, 2001)

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and for epilepsy (Loiseau *et al.*, 1990, Hauser *et al.*, 1991, Thomas, 1997, Anonymous, 2003, Rowan, 2000). Epilepsy occurs in about 1% of patients aged more than 65 years (about one quarter of newly diagnosed epilepsies) (Anonymous, 2003, Rowan, 2000, Sirven, 2001, Masnou, 2001, Peinemann and Stefan, 1998, Van Cott, 2002, Stephen and Brodie, 2000, Tallis *et al.*, 2002, Trinka, 2003). In this population, poststroke epilepsy is predominant, but tumoral, traumatic and neurodegenerative pathologies are more or less evenly distributed, each one estimated at about 10% of cases (Anonymous, 2003, Rowan, 2000, Sirven, 2001, Masnou, 2001, Peinemann and Stefan, 1998, Van Cott, 2002, Stephen and Brodie, 2000, Tallis *et al.*, 2002, Trinka, 2003). However, it is important to note that, contrary to immediate identification of an etiology associated with the beginning of epilepsy (stroke, intracranial neoplasia or post-traumatic sequel), there is no reliable anatomic marker for the degenerative process. A causal relationship between a dementing process and epilepsy can only be evidenced retrospectively, with progression of the disease, and can remain undetected within the scope of a crossover study. Thus, the high ratio of late-onset epilepsy classified as "cryptogenic" in studies on older patients (between 11 and 52% as quoted in a recent review of the literature) (Granger *et al.*, 2002) could be due to this bias. A study involving 341 first seizures occurring after age 60 linked these seizures with dementia in 7% of cases, while 32% were classified as cryptogenic (Granger *et al.*, 2002). When epilepsy is defined as at least two unprovoked seizures, 11.7% of epilepsies starting in elderly subjects are attributed to dementia (Van Cott, 2002). Keeping in mind the reservations expressed above concerning the etiologic category "cryptogenic" (at least in elderly), it can be considered that the 10% figure emerging from studies underestimates the contribution of degenerative pathology to epilepsy in older patients.

In practice, systematic assessment of cognitive functions after an initial seizure in an elderly patient whose etiologic investigations (including brain imaging) are negative constitutes a reasonable approach, particularly since numerous tests (such as Folstein) are now available and easy to perform in neurological departments.

Neurodegenerative disorders in adults: relation to epilepsy

Alzheimer's disease

Alzheimer's disease (AD) increasingly constitutes a large amount of cases seen by neurologists, and Epileptology specialists. It is estimated that about 10% of the population, aged over 65 years, is likely to be affected by this disease. After the age of 65, the incidence and prevalence of AD doubles every 5 years (McCullagh *et al.*, 2001). Surprisingly, epilepsy has been the subject of only few studies in this population. Neither textbooks in the field of epileptology (Ettinger and Devinsky, 2002, Wyllie, 2001, Meinardi, 2000, Thomas and Arzimanoglou, 2000) nor those on Alzheimer's disease (Richter and Richter, 2004, Growdon and Rossor, 1998, Mendez and Cummings, 2003), contain chapters dealing with this etiology, with its specific management, etc.

And yet, several indicators suggest that AD represents a risk factor for the onset of epilepsy. In a prospective study of 44 subjects clinically suspected of having advanced AD, and followed for 90 months, seven (16%) had at least one generalized tonic-clonic seizure, while no seizure was seen in the control group studied for the same period of time (Romanelli *et al.*, 1990). A retrospective study assessing epidemiologic data from Rochester, Min, showed that the presence of AD multiplied six times the risk of epileptic seizures, a risk that is even higher for other types of dementia (Hersdorffer *et al.*, 1996). In contrast to the previous study, which suggested a particular relation between the advanced stage of AD and seizure onset, in the Rochester study seizures were seen in some cases within the first 6 months of the disease, demonstrating the possibility of early co-morbidity (Hersdorffer *et al.*, 1996). In the population over 55 with dementia in a psychiatric department, prevalence of recurrent seizures was 9.1%, with an average incidence of 2.3 seizures per year for patients with epilepsy (McAreavey *et al.*, 1992).

The possible lack of precision associated with the use of clinical diagnostic criteria has led some authors to make retrospective studies of epileptic seizure prevalence in autopsy series where an AD diagnosis was confirmed. In the Rochester series, the neuropathological diagnosis of AD was associated with a risk of epilepsy ten times greater than that of subjects without dementia (Hauser *et al.*, 1986).

In a descriptive study comprising 56 patients whose diagnosis was also confirmed at autopsy, 11% had presented generalized tonic-clonic seizures during disease evolution (Förstl *et al.*, 1992). Another study reported 77 epileptic subjects (17%) out of 446 study participants whose AD was anatomically confirmed (Mendez *et al.*, 1994). Thus, the figures obtained based on autopsy series are similar to those obtained from clinical studies. Therefore, an estimate of 10% of epileptic subjects (with partial or generalized seizures) in the population diagnosed with AD, or with unspecified dementia, is a reasonable estimate. It is interesting to note, as does the preceding section, that about 10% of epilepsies in elderly subjects are related to a dementia, and that the same ratio (10%) of patients with dementia seems to suffer from epilepsy. Based on these figures and taking into account demographic projections in France, epilepsy associated with AD could concern 40 000 subjects in the years to come, that is, 20% of the overall epileptic population. This impressive figure contrasts with the absence of reference works on the subject, as we pointed out earlier.

Little information is available concerning the types of epileptic seizures associated with AD. The most common seizures reported are generalized tonic-clonic, but this could be the result of a bias related to the retrospective nature of most of the studies cited above. Partial seizures limited to a subjective aura or to blanking out with oral automatisms can also be difficult to diagnose, and difficult to recognize by the patient's family, given the existing mental deterioration. However, a complex partial status epilepticus was reported in two patients, aged 71 and 85 years; with autopsy-confirmed AD (Armon *et al.*, 2000). The status was the revealing symptom of dementia in one patient; the second had been diagnosed with dementia 5 years earlier.

Association with myoclonic seizures is also frequently reported. But it is important to underscore that although myoclonus is relatively frequent (about 10%) in the course of Alzheimer's disease (Hauser *et al.*, 1986, Mayeux *et al.*, 1985, Bakchine *et al.*, 1989, Caviness, 2003), and contributes to an unfavorable evolution prognosis (Förstl *et al.*, 1992), it is not always epileptic in origin, and can occur in two different populations, as was the case in the Rochester study (Hauser *et al.*, 1986). This risk of confusion could be explained by the difficulty of distinguishing between myoclonus of an epileptic nature (that is, associated with generalized or focal spike waves and polyspike-wave discharges), and cortical myoclonus that can only be confirmed when EEG back-averaging reveals a cortical event previous to muscle contraction (Caviness, 2003, Vercueil and Kreiger, 2001).

In AD, distal low-amplitude cortical myoclonus reproduce a classic minipolymyoclonus pattern which is difficult to distinguish from tremors (Wilkins *et al.*, 1985, Hallett and Wilkins, 1986). At present, no data in the literature allow us to state with certainty that minipolymyoclonus is a risk factor for the onset of epileptic seizures.

Moreover, confounding factors are not rare and they may interfere with neuropathological results. The lowering of the epileptogenic threshold with secondary seizures emergence, observed in patients treated with neuroleptics is an example. In one study, the average dose of neuroleptics was higher in the group with seizures than in the group without seizures (McAreavey *et al.*, 1992). The ratio of pathologic co-morbidity associated with AD is high because of the age of affected patients; for example, 45.5% of cases presented cerebral atheroma with secondary ischemic parenchymal lesions in an autopsy series (Fu *et al.*, 2004). In fact, cerebrovascular pathology is the major cause of epilepsy in the elderly. But mixed dementias do not appear to be associated with a particularly high incidence of epileptic seizures (Zekry *et al.*, 2002).

In practice, the presence of epilepsy in a patient with AD is associated with higher mortality rates (Chandra *et al.*, 1987), although accidents do not seem to occur more often in this population (McAreavey *et al.*, 1992). Onset of epilepsy in the course of AD could be associated with an unfavorable evolutional profile (Volicer *et al.*, 1995), although this result was not found in the studies cited above (Hersdorffer *et al.* 1996, McAreavey *et al.*, 1992, Hauser *et al.*, 1986, Förstl *et al.*, 1992, Mendez *et al.*, 1994). Therapeutic management will therefore be based on two major points: first, the epilepsy is relatively inactive and has only moderate influence on the patient's functional status; second, given the presence of cognitive impairment and associated therapies, clinical tolerance of the antiepileptic drugs should take priority, at the risk of aggravating the dementia syndrome (Kowh *et al.*, 2003). From this point of view, therapeutic choice follows criteria similar to the pharmacological principles applying to older patients (Leppik and Birnbaum, 2002).

Within the spectrum of Alzheimer's disease: Down syndrome, hippocampal sclerosis with dementia, early-onset AD, epilepsies simulating AD

Epilepsy is frequently encountered in infants and children with ***Down syndrome*** and may clinically manifest with features suggestive of West or Lennox-Gastaut syndrome. After the third decade, adults with Down syndrome present a dementing process with a neuropathological profile similar to that observed with AD (Lai and Williams, 1989).

In the latter case, prevalence of epilepsy rises rapidly with age (Pueschel *et al.*, 1991), reaching 46% after the age of 50 years (McVicker *et al.*, 1994). In a study involving 289 cases, dementia prevalence increased with advanced age (OR 3,56, 1,2-11,57 to 95% IC) and was associated with seizures (OR 9,579, 3-79-26,18 to 95% IC) and with myoclonus (13% in a population with dementia, as opposed to 0.8% in a population without dementia) (Tyrrell *et al.*, 2001). Late-onset epilepsy in Down syndrome is well characterized; associating myoclonic and generalized tonic-clonic seizures, with EEG showing generalized spike waves, so that the designation "senile myoclonus epilepsy" has been proposed for this diagnosis (Genton and Paglia, 1994). The term, "Down syndrome late-onset myoclonic epilepsy", was also proposed on the same basis (Möller *et al.*, 2001, Li *et al.*, 1995). In this context, an aggravating effect of phenytoine was reported, with the aggravation concerning the cognitive functions more than the epilepsy *per se* (Tsiouris *et al.*, 2002).

Dementia with "pure" hippocampal sclerosis has been described recently (Ala *et al.*, 2000, Mahieux, 2003). The subjects were patients with dementia whose autopsy showed no lesion other than severe hippocampal degeneration with gliosis, affecting particularly the CA1 segment and the subiculum.

This neuropathologic picture was found in 0.4% of the brains of subjects with dementia, supplied by one bank

(Ala *et al*. 2000). Unilateral hippocampal sclerosis without dementia is well-known by epileptologists as being a major finding in patients with the "classic" picture of temporomesial lobe epilepsy. Rare cases of epilepsy in the course of dementia with pure hippocampal sclerosis have been reported (Joseph *et al.*, 2003, Corey-Bloom *et al.*, 1997), but current data do not allow us to suppose that epilepsy prevalence in his patients population is different from that observed in patients with AD (Leverenz *et al.*, 2002).

Early-onset AD is the form of the disease on which genetic research has shed the most light. Different mutations of Presenilin 1 (PS1) have been found in a large proportion (up to 50%, according to studies) of early-onset AD with autosomal dominant transmission (Rocchi *et al.*, 2003.
Several families carrying different PS1 mutations presented epilepsy with myoclonus (Ezquerra *et al.*, 1999, Lopera *et al.*, 1997, Axelman *et al.*, 1998, Harvey *et al.*, 1998, Crook *et al.*, 1997, Fox *et al.*, 1997), compatible with a syndromic diagnosis of adult progressive myoclonic epilepsy (Melanson *et al.*, 1997). Cases of PS2 mutation are more rare, but association with epilepsy has also been reported in this context.
Finally, it is useful to remember that certain epilepsies can simulate AD. Three adult patients with memory problems progressing over one to four years, had deterioration of their cognitive performance as assessed by the Wechsler scale. Administering antiepileptic treatment, or modifying this treatment when epilepsy was known to exist, made it possible to correct the deficits observed (Hogh *et al.*, 2002). Other similar observations exist and indicate that an epileptic etiology should always be considered when faced with certain atypical presentations of dementia (Sinforiani *et al.*, 2003, Walstra *et al.*, 1997).

Frontotemporal dementia

Frontotemporal dementias (FTD) constitute a group of disorders with a common semiology based on predominant frontal and anterior temporal lobe involvement, with neuropathologic damage distinct from AD (Pasquier *et al.*, 1998). The prevalence of these disorders represents about 15% of patients with dementia (Miller, 1997), or 1 FTD for 6 AD (Pasquier *et al.*, 1998). No studies have examined the incidence of epilepsy in this population in particular, but descriptive studies of large series have not reported this co-morbidity. Subgroups of FTD: semantic dementia, primary progressive non-fluent aphasia, and frontal dementia (formerly Pick's disease) show no specific link with epilepsy either. However, frontotemporal dementia with parkinsonism linked with chromosome 17 (FTD-17q), first described in 1994 (Wilhelmsen *et al.*, 1994), has been associated with epilepsy repeatedly (Sperfeld *et al.*, 1999, Foster *et al.*, 1997), although epilepsy is not part of the classic clinical profile (Sillantini *et al.*, 2000, Hodges and Miller, 2001).

Creutzfeldt-Jakob disease

Myoclonus and epileptic seizures are often associated with Creutzfeldt-Jakob disease (CJD).
In a series of 230 sporadic cases published in the mid eighties, 8% of subjects had epileptic seizures in the course of the disease, while myoclonus was present in 88% of cases (Brown *et al.*, 1986).
Initial clinical presentation of the disease included epileptic seizures in 0.4% of cases only. In a more recent series, epilepsy prevalence reached 12% of cases (Poser *et al.*, 1999). When epilepsy revealed the disease, epilepsia partialis continua (Lee *et al.*, 2000, Parry *et al.*, 2001), partial status (Rees *et al.*, 1999, Fernandez-Torre *et al.*, 2004) or generalized status epilepticus (Neufeld *et al.*, 2003) have been reported. In the presence of periodic generalized or lateralized EEG abnormalities (Brown *et al.*, 1986, Poser *et al.*, 1999, Au *et al.*, 1980, Chiofalo *et al.*, 1980), a mistaken diagnosis of status epilepticus could be made as well, particularly when advanced cognitive deterioration is present. The distinction between non convulsive partial status epilepticus and periodic lateralized activity can be subtle, theoretically determined by a 1 HZ difference that can seem arbitrary (*figure 1*).
Other prionopathies are exceptionally associated with epilepsy: in the new CJD variant linked with bovine spongiform encephalitis, epileptic seizures are not reported. Frontal status epilepticus was observed in a familial form of CJD linked with a mutation in codon 129 of the prion protein (Dananchet *et al.*, 2001). In fatal familial insomnia or Gerstmann-Straussler-Schenker disease, epilepsy seems to be exceptional.

Parkinson's disease and Parkinsonian syndromes

Parkinson's disease is not associated with epilepsy. Given the relatively high prevalence of epileptic disorders and Parkinson's disease and their long-term evolution, a fortuitous coexistence is to be expected and can be evaluated. A simple cross calculation of the prevalence of each disorder in the elderly population results in a figure of one or two cases for 100 000 individuals over the age of 60, a very low percentage which explains why co-morbidity studies do not detect this association (Bodenmann *et al.*, 2001, Li *et al.*, 1985) except in rare cases (Gaitatzis *et al.*, 2004).
On the other hand, in the rare cases where association of the two diseases was observed, several authors found it interesting to point out a certain opposition between the respective progressions of each disease. Thus, the development of a Parkinsonian syndrome in an epileptic patient seems to decrease seizure frequency. This phenomenon was observed by Yakovlev in 1928 in post-encephalitic Parkinson patients who initially presented convulsive seizures, and in whom the onset of Parkinsonian led first to a reduction in seizures and then to their disappearance (Yakovlev, 1928).

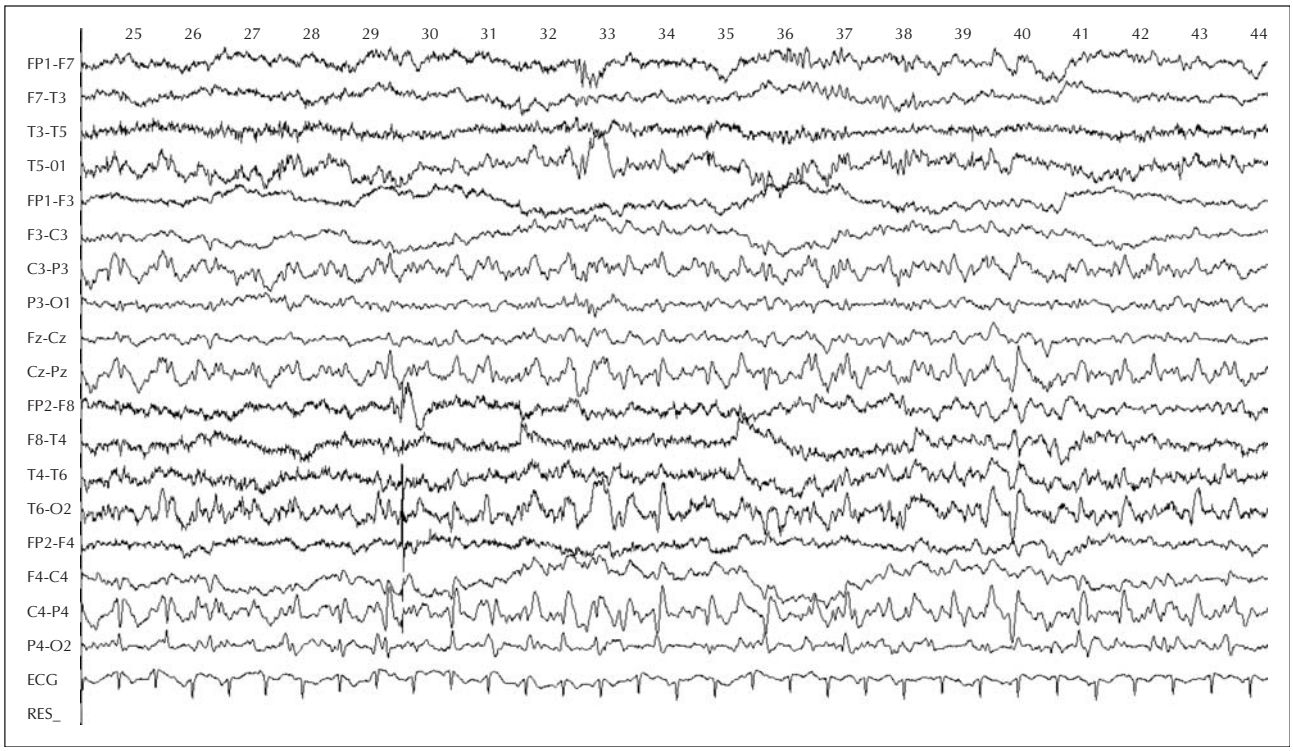

Figure 1. A 63-year-old woman with a several months' history of progressive visual disturbances and left upper extremity awkwardness. Polygraphic recording revealed negative myoclonus in the left upper limb in addition to presence of a continuous periodic activity with sharp waves in the right centroparietal region. Clinically, there was dystonia and apraxia of left upper limb. Neuropathological studies confirmed suspected Creutzfeldt-Jakob disease.

Urechia and Elekes, and later Urechia and Mihalescu (Urechia and Mihalescu, 1928), reported the case of a patient who had had epileptic seizures since the age of two years, and whose seizures disappeared when he developed Parkinson's disease at age 42. Pathology revealed lesions of the substantia nigra, globus pallidus and striatum. Genuine cases of Parkinson (clinically confirmed) appearing in an epileptic context are rarer (De Angelis and Vizoli, 1984, Jimenez-Jimenez *et al.*, 1991, Vercueil, 2000, Scarpino *et al.*, 1990). In these subjects, two observations have been made: first, seizure occurrence is associated with a transient reduction in the clinical signs of Parkinson's disease (De Angelis and Vizoli, 1984, Jimenez-Jimenez *et al.*, 1991, Vercueil, 2000), an observation compatible with the positive effect identified in the course of electroconvulsive therapy given to depressed Parkinsonian patients (Lebenshon and Jenkins, 1975, Moellentine *et al.*, 1998, Pridmore *et al.*, 1995); and second, a reduction in seizure frequency in the course of the development of parkinsonian symptoms (Vercueil, 2000).

This last observation is the more interesting of the two, because it suggests that basal ganglia play a role in controlling epileptic seizures, although numerous questions are yet to be clarified (Vercueil, 2000; Vercueil and Hirsch, 2002).

Myoclonus of cortical origin has been observed in Parkinson's disease; some myoclonias were triggered by intermittent photic stimulation, leading to the consideration of possible photosensitive epilepsy (Scarpino *et al.*, 1990, Henneberg *et al.*, 1998). In certain forms of multiple system atrophy (MSA), myoclonia triggered by intermittent photic stimulation have been reported (Obeso *et al.*, 1985). The literature is still vague about the differential diagnosis of photic myoclonus, reflex cortical myoclonus induced by visual stimulation, photomyogenic response and photomyoclonic response. These questions are not within the scope of this article. However, it should be remembered that photomyogenic response is not unusual in the elderly population, and that it can be seen in Parkinson patients. In terms of the EEG, this response is associated with predominantly anterior muscular potentials sometimes mimicking activity of epileptic origin (*figure 2*).

Certain of the figures found in articles concerning "photosensitive" Parkinson patients bring to mind this diagnosis (Scarpino *et al.*, 1990, Henneberg *et al.*, 1998).

In publications on Parkinson "plus" syndromes, epilepsy is sometimes mentioned (Daniel *et al.*, 1995, Nygaard *et al.*, 1989, Peset *et al.*, 2001), but based on the information provided, it is difficult to exclude the possibility of acute

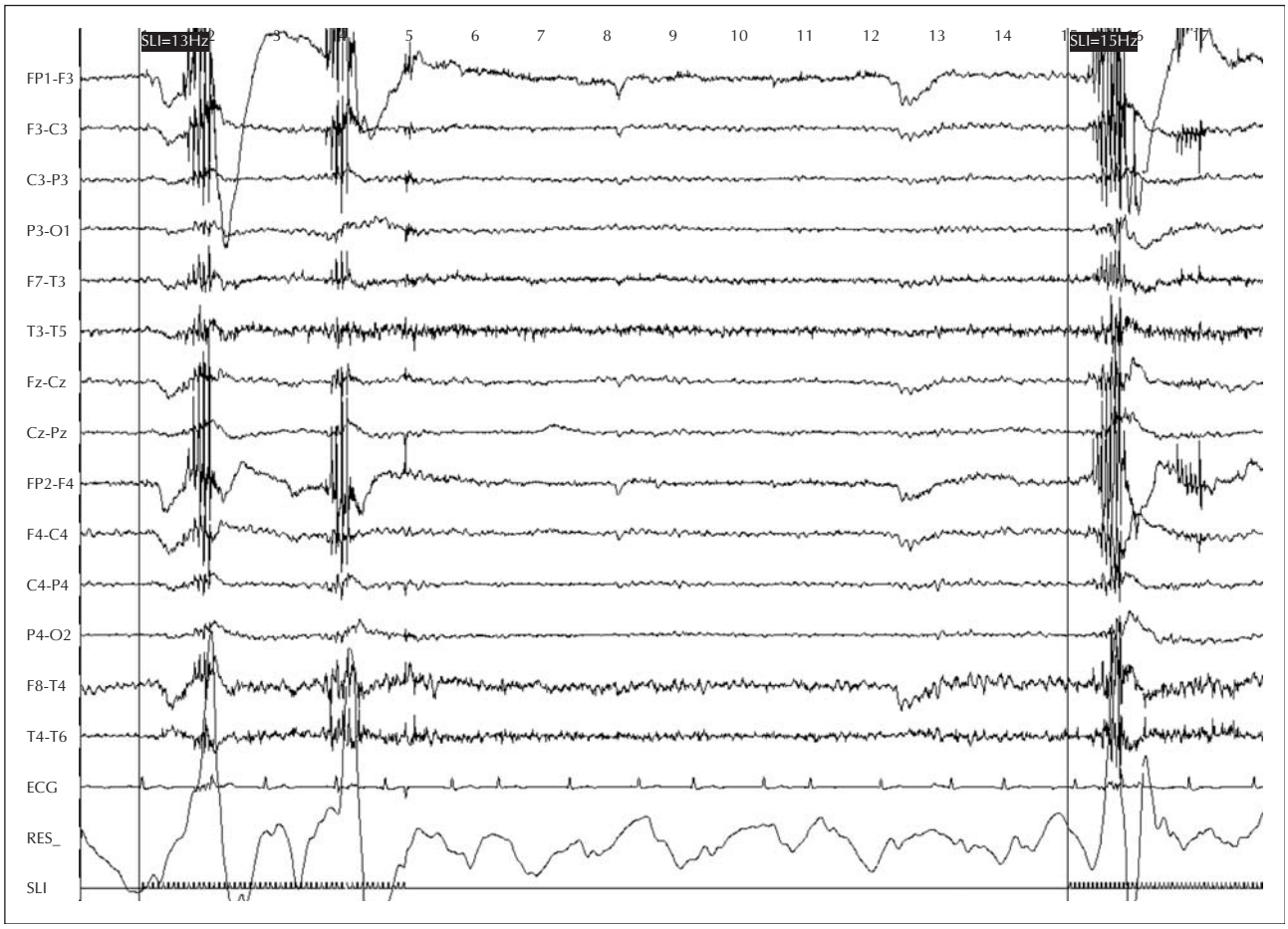

Figure 2. A 74-year-old man, presenting dopamine resistant Parkinson disease. Hospitalized following an episode of loss of consciousness. EEG shows no abnormalities except at intermittent photic stimulation (IPS). During IPS, large amplitude axial and appendicular myoclonia associated with anteriorly predominant muscular potentials are recorded: photomyogenic response.

symptomatic seizures in debilitated patients having a dramatic progression of their disease.

In these pathologies (Parkinson "plus"), neuropathological lesions, no longer limited to the basal ganglia region as they would be in Parkinson's disease, damage cortical function and are therefore more likely to trigger epileptic activity.

Neurodegenerative disorders in young adults

In young adults with neurodegenerative pathologies, epilepsy occurs more often. It can take the form of partial seizures or isolated generalized tonic-clonic seizures, but in adults a complete picture of progressive myoclonic epilepsy, with epileptic seizures, myoclonia and cognitive deterioration, can also be observed. In this context, etiologies seen in children are exceptionally observed in adults (Genton *et al.*, 2002), but certain etiologies, such as early-onset Alzheimer linked to presenilin 1 mutations, mentioned earlier, might be more specific (Melanson *et al.*, 1997).

The adult form of ceroid lipofuscinosis, or Kufs' disease, has been subdivided into two types, depending on clinical presentation: type B does not include epilepsy, while type A conforms to the profile of adult progressive myoclonic epilepsy (Berkovic *et al.*, 1988). This disorder is characterized by visual problems with gradual progression, infrequent generalized tonic-clonic seizures, incapacitating reflex cortical myoclonus and secondary dementia, with evolution toward death on average 10 years after onset (Genton *et al.*, 2002, Berkovic *et al.*, 1988, Wisniewski *et al.*, 2001).

EEGs record generalized spike wave discharges and photosensitivity present from the lowest frequencies of photic stimulation (*figure 3*). Often, diagnosis can only be made after cerebral biopsy.

Epilepsy can manifest in adults with mitochondriopathies. In a series of 14 patients with disease onset between the

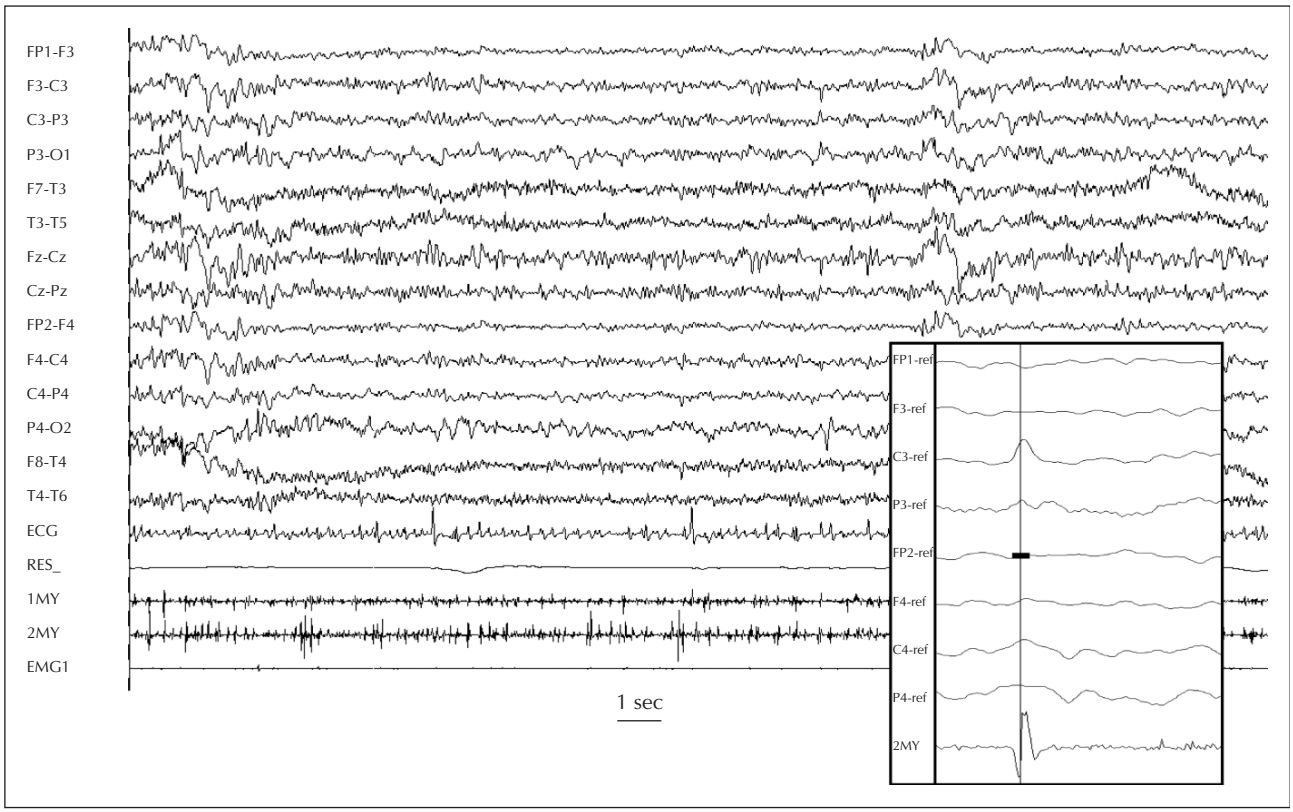

Figure 3. A 35-year-old woman, presenting a progressive profile of dementia with visual problems, rare generalized tonic-clonic seizures, and incapacitating action myoclonus (Kufs' disease) confirmed by neuropathologic exam (cerebral biopsy). EEG shows presence of spike waves at vertex in addition to a photoparoxystic response provoked by IPS. Back-averaging of the right upper limb myoclonus reveals previous positive wave in left central region.

ages of seven and 44 years, three presented a progressive myoclonic epilepsy profile due to myoclonic epilepsy with ragged red fibers (HERRF); in two other subjects who were carriers of MERRF mutations, the clinical presentation was atypical, but initially compatible with progressive myoclonic epilepsy (Canafoglia *et al.*, 2001).

Four of five patients presenting a MELAS profile had partial motor seizures and the fifth had generalized seizures from the start (Canafoglia *et al.*, 2001). A previous series mentioned possible onset of the disorder between the ages of three and 65 years (Roger *et al.*, 1991). In one recent case, a 29 years old patient was found to have a mitochondrial DNA mutation, in a context of generalized seizures, myoclonia, psychiatric problems and myopathy (Amemiya *et al.*, 2000). In Huntington's disease, progressive myoclonic epilepsy is seen in the infantile forms (Genton *et al.*, 2002, Garrel *et al.*, 1978). Onset of epilepsy in adulthood appears to be rarer, but has been reported (Bengel *et al.*, 1997). Onset of progressive myoclonic epilepsy at age 24 was seen in a subject presenting a mutation in the neuroserpin gene (Yazaki *et al.*, 2001), a fact which indicates that neuroserpinopathies should be classified among the possible causes of progressive myoclonic epilepsy in adults. Dentatorubral pallidolyusian atrophy (DRPLA) associates dementia with ataxia, abnormal movements and epilepsy (Tsuji, 2000). Onset has been observed in adulthood, up to age 69 (Genton *et al.*, 2002).

Among spinocerebellar atrophies (SCA), epilepsy was seen in nine of the eleven members of two families with CAG trinucleotide repeat of the TBP gene of SCA type 17 (Filla *et al.*, 2002, De Michele *et al.*, 2003). In Wilson's disease, epilepsy is frequent, and was found in 6% of subjects in a large series (Dening *et al.*, 1988).

Principles of epilepsy management in the course of a neurodegenerative disease in adults

Once the possibility of an acute symptomatic seizure has been eliminated (essentially, hypoglycemia, hyponatremia, toxic and drug-related causes), whether or not to start an antiepileptic treatment must be determined. Although there is no consensus on the subject, medical management can be based on the following principles:

1) Introducing antiepileptic therapy in elderly patients is complicated by numerous pharmacodynamic factors: associated therapies are common and drug interactions are frequent; albuminemia and renal clearance are diminished; adipose mass increase can augment the distribution volume of liposoluble drugs, and can modify their half-life; hepatic metabolism is altered, etc.;
2) Neuropsychic sensitivity to psychotropes (including antiepileptics) is increased, especially in the presence of dementia: sedation effect is increased, confusion can rapidly occur, psychiatric symptoms or cognitive aggravation can be directly related to treatment;
3) Severity of the epilepsy must be assessed. Studies have shown that seizures do not modify morbidity, or modify it very little (including fall-related injury), in institutionalized, supervised populations.
Medical treatment is therefore conditioned by these considerations. The treatment of choice allows adequate control of critical manifestations, with limited toxicity and drug interaction, as well as acceptable neuropsychic tolerance. In reference to older populations, many review articles have discussed the choice of treatment (Thomas, 1997, Anonymous, 2003, Rowan, 2000, Sirven, 2001, Masnou, 2001, Peinemann and Stefan, 1998, Van Cott, 2002, Stephen and Brodie, 2000, Tallis *et al.*, 2002). These articles recommend monotherapy and underline the benefits of large-spectrum antiepileptic drugs such as valproate and lamotrigine, or medications with limited cognitive effects, such as phenytoine and gabapentine. Few original studies evaluating antiepileptic therapy tolerance and effectiveness have pertained specifically to the elderly, with the exception of lamotrigine, which was found to be just as effective and better tolerated than carbamezepine in this population (Brodie *et al.*, 1999). Among the new antiepileptics, levetiracetam, topiramate and oxcarbazepine have not been studied in elderly populations.
Very gradual introduction of treatment, close supervision of biological parameters and careful clinical assessment of drug tolerance should be applied systematically. In the context of neurodegenerative disease, therapy effectiveness can be difficult to determine, and EEG monitoring can prove to be of little help (abnormalities may be related to the underlying degenerative process). Recourse to indirect indicators of effectiveness (reduction of falls related trauma, improvement of attention, etc.) is a good alternative. There is no doubt that epilepsy in the context of neurodegenerative pathology in young adults requires a different management approach. This approach is more active, to match the aggressive nature of the pathologic process; therefore, recourse to pharmacological combinations is often required. In this population, biologic and clinical tolerance of these treatments is generally greater, and rational polytherapies are often indicated; progressive myoclonic epilepsies are a case in point (see article by Pierre Genton in this issue, pp. S37-43).

Conclusion

It is surprising to see to what extent epilepsy in neurodegenerative disorders remains underestimated. Few original articles deal with it, and review article still outlining major diagnostic and treatment principles are lacking.
Nevertheless, epilepsy is part of the clinical picture of some of the most common neurodegenerative pathologies, including Alzheimer's disease. Neurologists will probably deal with this disease to a growing extent in the future, and will need recommendations for epilepsy management in this setting. □

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