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Can we predict refractory epilepsy at the time of diagnosis?

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ABSTRACT – The early prediction of intractability is a major challenge in epileptology. Some prognostic factors have been pointed out, most of which simply underlined that partial epilepsy is more difficult to control than idiopathic generalized epilepsy (IGE). Indeed, the main predictors are the presence of a brain lesion demonstrated by neuroimaging or suggested by a neurological deficit or a developmental delay, as well as electroclinical evidence of non idiopathic partial epilepsy. Little is known about the relationship between the location of the epileptogenic area and the chance of being seizure-free in patients with partial epilepsy. Some data suggest that temporal lobe epilepsy (TLE) is more difficult to control than other partial epilepsies, but this might only reflect the prognostic impact of hippocampal sclerosis. Indeed, several studies have shown that the majority of patients with MRI evidence of hippocampal sclerosis develop refractory epilepsy. This observation also applies to patients with malformation of cortical development (MCD). The response to the first AED is another early predictor of refractory epilepsy. At the time of diagnosis, several prognostic factors are available to predict drug resistance, but further studies are still needed to better delineate the specific role of each of these factors, and to offer a more accurate prediction of long term seizure outcome.

Key words: prognosis, treatment, syndrome, epilepsy, MRI, risk-factor

Up to 30% of patients with epilepsy do not undergo remission despite adequate antiepileptic drug treatment (AED) (Hauser *et al.* 1998, Kwan and Brodie 2000, Hart *et al.* 1990). The early identification of this population remains a major issue, even though a number of risk factors have been previously delineated. The main predictors for seizure relapse in adults are the presence of an abnormal EEG, an abnormal neurological examination, partial seizures, a known etiology, an abnormal CT scan or MRI, Todd's paralysis, and a developmental delay (Hart *et al.* 1990, Elwes *et al.* 1984, Sillanpää 1993, Sander 1993, Berg and Shinnar 1991, Hauser *et al.* 1990). Most of these factors reflect the presence of a localized-related form of epilepsy (Mattson *et al.* 1996). The prognostic value of other factors such as age at onset is controversial. A more precise delineation of early risk factor in the different groups of patients with epilepsy is still needed, provided the heterogeneity of epileptic syndromes and of their respective prognosis (Kwan and Brodie 2000, Sander 1993, Semah *et al.* 1998).

Role of the epileptic syndrome

Epileptic syndromes carry various prognosis in adults and children. For

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example, the majority of patients with juvenile myoclonic epilepsy (JME) are seizure-free when treated with adequate AEDs (Wolf and Inoue 2002), such as valproate or lamotrigine (Prasad *et al.* 2003), whereas the majority of patients with mesial temporal lobe epilepsy (MTLE) remained refractory to most antiepileptic drugs (Semah *et al.* 1998). There is however a subset of patients with drug resistant IGE. In a study conducted in 155 patients with newly diagnosed JME, Gelisse *et al.* reported that 10% continued to suffer seizures despite adequate therapy and lifestyle (Gelisse *et al.* 2001). Unfortunately, they could not find any significant prognostic factor of drug resistance in that population (Gelisse *et al.* 2001). In patients with partial epilepsy, response to treatment might evolve over time, with approximately half of refractory patients who will develop drug resistance after at least five years of treatment (Berg *et al.* 2003). When looking at the prognostic criteria of intractability hitherto described, such as age at onset, remote symptomatic epilepsy, status epilepticus, focal EEG abnormalities, abnormal CT scan or MRI, Todd's paralysis, complex partial seizures, and an abnormal neurological examination (Cockerell *et al.* 1997, Berg *et al.* 1996, Berg *et al.* 2001), one could conclude that most of these predictors reflect the presence of a symptomatic or cryptogenic epilepsy. Accordingly, in a large prospective hospital-based study conducted in 2200 patients, we found that the chance of being seizure-free significantly depended on the epileptic syndrome, *i.e.* 82% in idiopathic generalized epilepsy, 45% in cryptogenic partial epilepsy, and 35% in symptomatic partial epilepsy (Semah *et al.* 1998).

Role of the etiology of partial epilepsy

A few studies have focused on this issue, showing a clear relationship between the etiology of the epilepsy, or of the associated brain lesion, and the likelihood of seizure control with AEDs (Semah *et al.* 1998, Semah *et al.* 2002, Stephen *et al.* 2001). These findings largely rely on the development of MRI, accounting for the fact that studies performed prior to the systematic use of optimal MR images did not find correlation between the etiology and the prognosis of partial epilepsy (Hauser *et al.* 1998). Results from our own serie suggested that the prognosis of partial epilepsy was more closely related to the type of lesion than to the lobar localization of the epileptogenic zone (Semah *et al.* 1998). Drug resistance was observed in 97% of patients with HS and an associated malformation of cortical development (MCD) in the temporal lobe, 89% of patients with HS only, 76% of those with MCD only, 65% of patients with brain injury, 50% of those with a vascular malformation, and only 46% of patients with post-stroke epilepsy. In patients with TLE and isolated hippocampal abnormalities, those with HS were more likely to develop drug resistance than those with hippocampal malformations (Semah *et al.* 2002). Another study of 550 adult patients with epilepsy, including 43% with recurrent seizures, demonstrated the same findings (Stephen *et al.* 2001). HS and MCD were associated with the poorest prognosis, with 58% and 46% rates of drug resistance, respectively, followed by tumor (37%), stroke (33%), and arteriovenous malformations (22%). Van Paesschen and colleagues also clearly showed that patients with newly diagnosed epilepsy and HS had a worse prognosis than those with other MRI abnormalities or normal findings (Van Paesschen *et al.* 1997). Some isolated case reports also suggest that the type of MCD influences the prognosis of epilepsy but this needs to be confirmed by controlled studies. For instance, seizures associated with focal cortical dysplasia and dysembryoplasic neuroepithelial tumors seem to be more difficult to control than those symptomatic of other malformations, such as heterotopia. In line with the results of previous series, patients with post-stroke epilepsy were found to present a two fold higher rate of 5 years-remission than patients with brain tumors (Cockerell *et al.* 1997). In a recent series of 581 stroke patients aged 18 to 55, including 20 with a first late seizure, only 11 experienced seizure recurrence while on AED treatment, most of whom became eventually seizure free (Lamy *et al.* 2003).

Role of the localization of the epileptogenic zone

In our study conducted in 2200 patients, those with TLE were more frequently drug-resistant than patients with frontal, occipital or parietal lobe epilepsy (Semah *et al.* 1998). However, multivariate analysis showed that the main predictor of intractability was the presence of hippocampal sclerosis, rather than the temporal lobe origin of seizures per se.

Role of the initial response to AED

An accurate prediction of intractability is probably easier to perform a few months after the initiation of treatment than at the time of the first visit, due to additional available data regarding the type and aetiology of the epileptic syndrome, as well as the efficacy of the first AED. Indeed, a recent study in children has demonstrated that failure to respond to the first antiepileptic drug predicts the development of refractory epilepsy (Dlugos *et al.* 2001). The large National General Practice Study of Epilepsy (NGPSE) in the UK has also shown that one of the major prognostic factor was the number of seizures in the early months after presentation (MacDonald *et al.* 2000). In addition, some authors have suggested that the time elapsing between the onset of epilepsy and the first treatment, as well as the number of seizures before treatment, predicted the devel-

opment of drug resistance (Hauser *et al.* 1998, MacDonald *et al.* 2000). However, these data remain controversial. In a study including 479 children in Nova Scottia, Camfield *et al.* reported that the number of seizures before treatment, if less than 10, did not influence the chance of seizure control (Camfield *et al.* 1996).

Two large controlled studies have also demonstrated that introducing AED treatment after the first or the second seizure resulted in similar rates of long term seizure freedom (Musicco *et al.* 1997, Marson *et al.* 2005). Thus, early treatment does not seem to influence the prognosis of epilepsy, but response to first AED helps to predict the risk of further drug resistance.

Potential role of genetic predictors

Despite the sporadic and non idiopathic origin of the majority of refractory epilepsies, genetic susceptibility factors might participate to the development of this condition. In particular, gene polymorphisms could explain why apparently similar brain lesions will result in the development of drug resistance in some patients, but not in others. Two gene polymorphisms have been associated with AEDs refractoriness. They involve the $GABA_B$ receptor and the glycoprotein P170 (Pgp or MDR1 for multi-drug-resistance protein 1), respectively (Gambardella *et al.* 2003, Siddiqui *et al.* 2003). Regarding the $GABA_B$ receptor, an A/G polymorphism at position 1465 is responsible for a Gly489Ser substitution in a highly conserved region of the receptor, which thus might have functional consequences. Gambardella *et al.* reported that 17% of TLE patients have an A/G genotype, *versus* only 0,5% in their normal population (Gambardella *et al.* 2003). In addition, the A/G genotype was associated with a 6,47 *odds ratio* for developing drug resistance in this study (Gambardella *et al.* 2003). However, these findings could not be replicated in three recent independent studies (Ma *et al.* 2005, Tan *et al.* 2005, Salzmann *et al.* 2005). Regarding the Pgp gene, or ABCB1 gene (for ATP binding cassette subfamily B 1 gene), most studies have concentrated on the 3435C-T polymorphism, though other genetic variants were also described (1236C-T, 2677G-T). The 3435C-T polymorphism is silent, but associated with higher level of Pgp expression in various cell lines (enterocytes, CD56+). A C/C genotype at position 3435 was found to be associated with higher risk of drug resistance in two studies (Siddiqui *et al.* 2003, Zimprich *et al.* 2004), but again, this result could not be replicated in two other series (Tan *et al.* 2004, Sills *et al.* 2005). Thus, alike in many other fields, studies of gene polymorphism have yet failed to provide consistent results regarding the genetic susceptibility to develop refractory epilepsy. This remains however an exciting field of research which might proved fruitful in the future. □

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