Developmental delay and epilepsy

Nathalie Bednarek[1], Jacques Motte[2]

[1] Service de pédiatrie, Hôpital Alix-de-Champagne, Reims
[2] Hôpital Américain, Service de pédiatrie, Reims, France

ABSTRACT – Developmental delay can be associated with epilepsy. Epilepsy might be either the cause of the delay of acquisitions (epileptogenic encephalopathy) or only one additional manifestation, the consequence of the underlying neurological pathology (encephalopathy with epilepsy); it is therefore not the only factor responsible for delay. Within the framework of encephalopathies with epilepsy a rigorous diagnosis is necessary with, in particular a cutaneous examination (neuro-cutaneous syndromes), a precise clinical examination (anoxo-ischaemic sequelae of the perinatal period), an EEG, a cerebral magnetic resonance imaging (MRI) as well as the search for associated abnomalities (cardiac, renal...). There are also epileptogenic encephalopathies such as age-related syndromes: Hemiconvulsions-Hemiplegia-Epilepsy syndrome; Rasmussen's syndrome; Dravet's syndrome; myoclono-astatic epilepsy (Doose). Age at onset and type of seizures, as well as ictal and interictal EEG finding provide valuable hints for a specific diagnosis, while other investigation are usually not contributive. Developmental delay and epilepsy are frequently associated. One of the first steps to diagnosis consists in trying to establish the eventual causal role of the epilepsy. Answering this question may prove to be of primary importance for the choice of a therapeutic strategy and/or further etiological investigations.

Keywords: child, developmental delay, epilepsy, epileptic encephalopathy

Correspondence:
N. Bednarek
Service de pédiatrie,
Hôpital Alix-de-Champagne,
49 rue Cognacq-Jay,
51092 Reims cedex,
France
<nbednarek@chu-reims.fr>

Epilepsy and psychomotor delay often coexist and the choice of diagnostic investigations can be determined based on the type of delay presented by the child. In this context, two distinct disorders have been identified: encephalopathies with epilepsy, and epileptogenic encephalopathies. Genetic and neurodegenerative etiologies are not included in the following discussion.

Encephalopathy with epilepsy is characterized by the association of pre-existing overall developmental delay and epilepsy that appears at a subsequent point in the child's development.

Epileptogenic encephalopathy is characterized by psychomotor problems that progress and worsen, with the epilepsy constituting the major element of the clinical picture. In this context, neither a clinical examination nor brain imaging or other investigations (karyotype, metabolic work-up...) usually contribute to the diagnosis.

Encephalopathy with epilepsy: diagnostic work-up

General investigations

It is important to obtain a full personal and familial medical history, combined to a rigorous physical examination.

Recognition of the seizure type, ictal and interictal EEG findings during

N. Bednarek, J. Motte

sleep and awake contribute to the diagnosis. The diagnostic hypothesis will guide the selection of screening investigations for associated pathologies (visual investigation (OF, VEP, ERG); cardiac and renal ultrasound and a skeletal radiography). In the majority of cases, at least one MRI and electrophysiological investigations (EMG, NVC) will be performed, to better explore the underlying neurological disorder.

Examples: neurocutaneous syndromes

These syndromes characterized by the presence of cutaneous manifestations are leading causes of developmental delay with epilepsy. The first example is *Sturge-Weber syndrome* (1 in 10 000 births) with facial cutaneous angioma in the territory of the first trigeminal division (eyelid and upper quarter of the face) with associated pial and sometimes choroidal angioma. The pial angioma predominates in the occipital region, but can extend to the parietal or temporal region.

The angioma modifies the venous network, producing chronic venous ischemia at the cortical level and, secondarily, contributing to cortical atrophy. Leptomeningeal contrast enhancement at MRI can be difficult to distinguish initially, and the test must then be repeated. An EEG during the neonatal period shows low voltage activity on the side of the angioma.

Other neuroradiological signs are associated with this syndrome: localized cortical atrophy that can be progressive, intraparenchymatous calcifications indicating chronic venous ischemia, and unilateral hypertrophy of a choroid plexus indicating excessive pressure in the cerebral venous system. The SPECT can be more sensitive initially, showing a significant hypometabolism in the involved region. Mental retardation exists in 60% of all cases (Castroviejo and Diaz-Gonzalez 1993). The greatest risk associated with this syndrome is cerebral venous ischemia that can occur spontaneously during the period of the child development. Status epilepticus is another risk (Coley *et al.* 1998). In order to avoid the latter, preventive treatment with anticonvulsants is suggested by some authors (Ville *et al.* 2002).

Tuberous sclerosis is quite easy to recognize in patients with partial epilepsy, because of the presence of achromic stains as early as in the first two months of life, and in 80% of the cases during the first year of life. The tubers are visible immediately upon birth, and even prenatally as a T2 hypersignal at cerebral MRI. Other cutaneous signs exist in Bourneville's tuberous sclerosis, but they develop later: ungueal fibromas, facial angiofibromas, damage to connective tissue (shagreen patch) for example, occurring mostly after the age of 10 years. Cognitive problems or mental retardation are present in 38 to 80% of cases reported (Curatolo *et al.* 2002).

Incontinentia pigmenti is another phacomatosis that can be accompanied by very characteristic skin manifestations visible as early as the neonatal period. Four stages of evolution are described: first, maculopapular lesions and vesicular streaks at the inflammatory stage (in the newborn), mistakenly recalling herpes-type lesions. The particularity of these lesions is their linear distribution along the lines of Blascho, and their complete disappearance within 6 weeks. The second stage, called proliferative (or verrucuous-lichenoid) is associated with papillomatous lesions which replace the previous vesicles between the second and the sixth week of life. Hypereosinophilia is present at this stage. The third stage is characterized by an increase in melanin in the lesions, which become brick coloured (third to sixth month of life). In the last stage, called involutive, the pigmented stains regress and achromic stains or atrophic streaks appear. In incontinentia pigmenti, there are concomitant ungueal anomalies (dystrophy), as well as dental and ocular anomalies (myopia, microphtalmia).

Cerebral damage appears to be of ischemic nature (Hennel *et al.* 2003) with different consequences depending on the time of onset: microcephaly and gyration abnormalities (antenatal onset), cerebral atrophy and porencephaly for postnatal onset.

Motor signs

Motor signs can be related to ischemic sequelae of perinatal or antenatal origin. The study conducted by N. Senbil, which compared 74 children observed for two years (Senbil *et al.* 2002), estimated the frequency of epilepsy based on the associated motor dysfunction: epilepsy was present in 60.5% of children with tetraparesis, and in 22% and 8% of those with diplegia and hemiplegia respectively. The epilepsy was considered as a sign of severity of the underlying pathology. In 50% of cases, the age at onset of epilepsy was less than one year, and in 29% of cases seizures were present in the neonatal period. Seizures were mostly generalized tonic-clonic (45.2% of cases), partial (6%), and in 6% of cases the children had infantile spasms. Okurama (Okumura *et al.* 2000) studied seizure frequency based on lesion chronology, and did not find significant differences depending on the groups studied: when the lesion was prenatal 24% of children presented seizures, as compared to 39% and 25% of children with perinatal and postnatal lesions, respectively. Okurama simply noted the great frequency of febrile convulsions in children presenting a cerebral palsy (30% of cases). Gaggero (Gaggero *et al.* 2001) stressed the high incidence of epilepsy in children with infantile cerebral hemiplegia (30%). He identified pharmaco-resistance factors such as cortical malformations; great frequency of seizures; the polymorphic nature of seizures, particularly during the first two years of epilepsy; and epilepsy occurring after the age of 12 years and whose duration exceeds seven years.

Types of seizures

When clinical examination is normal, the types of seizures observed can be a clue suggesting a specific etiology. Examples are the presence of myoclonia or of gelastic seizures.

The presence of myoclonia may be suggestive of an inborn error of metabolism (non-ketotic hyperglycinemia, ceroid lipofuschinosis...), certain genetic etiologies (Angelman's syndrome, Rett's syndrome, or 4p-...) and brain anoxia. Certain epileptic syndromes can also be considered, such as infantile myoclonic encephalopathy (Aicardi), and Dravet syndrome. Gelastic seizures with fits of paroxystic laughter are strongly suggestive of a hypothalamic hamartoma, of Pallister-Hall syndrome (OMIM#146510), associating in addition to gelastic seizures, renal, auditory, cardiac, anal and genital abnormalities. Polydactyly with ungueal anomalies are markers of this syndrome. The responsible gene has been identified (gene GLI 3) in the 7p13 chromosomal region.

Interictal EEG

Finally, an interictal EEG can be helpful in the etiological work-up. For example, focal, high amplitude rapid rhythms could indicate a cortical malformation. Similar rhythms occurring for around 10 seconds during sleep, might suggest a Lennox-Gastaut syndrome. In the absence of anoxic events, burst-suppression pattern may suggest a non-ketotic hyperglycinemia, or a state of pyridoxine deficiency.

Brain MRI

It goes without saying that a brain MRI is mandatory in cases of epilepsy with encephalopathy, whether or not the clinical examination and the ictal and post-ictal EEG are contributive to a diagnosis.

Lissencephaly and Aicardi's syndrome are examples of cerebral malformations associated with encephalopathy.

Epileptogenic encephalopathy: diagnostic investigations

Definition

Epileptogenic encelopathy is characterized by the presence of psychomotor problems that are progressing and worsening with the epilepsy, in the setting of normal clinical and complementary investigations (*i.e.* brain MRI, karyotype and metabolic workup).

HHE (Hemiconvulsions, Hemiplegia and Epilepsy)

This syndrome was first described by Gastaut (Gastaut *et al.* 1957). The disorder typically begins in a febrile context, in children younger than six years (90% of cases before the age of two years) having no particular past medical history

Often a family history of epilepsy or febrile convulsions is reported. Improved management of convulsive status epilepticus chiefly by the administration of intrarectal diazepam since the 1960s probably explains the decrease of the syndrome's frequency in industrialized countries over the past 15 years (Chauvel and Dravet 2002).

The clinical picture is characterized by prolongued clonic seizures taking the form of status epilepticus with unilateral predominance, accompanied by hemiplegia. The seizures described initially could last between 30 minutes to 12 hours [9]. In a series described by Aicardi (Aicardi and Baraton 1971), status epilepticus lasted 24 hours or more in 31 cases, and less than six hours in the remaining cases. Convulsions could be unilateral, but could start on one side and diffuse to the other side, or could generalize from the beginning. Fever is present in 50 to 75% of cases. Seizures are accompanied by a more or less marked alteration of the level of consciousness and are followed immediately by hemiplegia on the predominant side of the seizure. In 20% of cases, the hemiplegia disappears within 12 months, with the possible persistence of a discrete pyramidal syndrome. Risk factors for hemiplegia include: seizure duration of over five hours, and young age (less than 18 months). There is often an associated cognitive impairment (Chauvel and Dravet 2002).

Brain imaging shows oedema and hemispheric atrophy controlateral to the hemiplegia. Angiographies were normal in 31 tested patients (Aicardi and Baraton 1971). Brain MRI makes it possible to exclude vascular and infectious aetiologies. On the affected side, the EEG shows slow-waves or discharges of rhythmic high amplitude slow waves, at two to three cycles per second. These discharges can diffuse to the contra lateral hemisphere. With evolution, it may persist as partial epilepsy that is most often temporal.

Pathogenesis of the HHE syndrome is still unknown, but appears to be similar to that of febrile convulsions (Chauvel and Dravet 2002).

Today, the incidence of this syndrome is low, probably due to improved prevention of infections in the infantile population of developed countries, and preventive treatment of febrile convulsions.

Rasmussen's syndrome

Rassmussen's syndrome usually presents with continuous partial seizures and progressive hemiparesis associated with progressive hemispheric atrophy (Hart and Andermann 2002). It constitutes one of the differential diagnoses of HHE syndrome

Average age at onset is five years, with extremes from 14 months to 14 years.

Convulsions are the initial manifestations with simple partial motor seizures occurring in most cases. In some

cases, seizures can initially present in the form of status epilepticus. Some patients present sensory motor seizures. The second characteristic of the syndrome is hemiparesis occurring progressively in the course of the first year. Other deficits can coexist (aphasia, dysarthria, visual deficits). The later forms of the syndrome (adolescence and adulthood) have a more favorable evolution. One third of the children have had a previous infection in the six months preceding the continuous partial seizures. Cerebrospinal fluid protein electrophoresis reveals a monoclonal or oligoclonal aspect resembling that observed in cases of chronic encephalitis. The etiopathogenesis of the syndrome is unknown: could it be that genetic or other factors increase the fragility of the blood-brain barrier?

With the disease evolution, there is a risk of bilateral diffusion of epileptiform discharges. Thus, functional hemispherectomy should be considered rapidly in cases where medical treatment fails.

Severe myoclonic epilepsy of infancy (Dravet syndrome)

This syndrome usually affects normal children with a family history of epilepsy (25% of cases) or of febrile convulsions (Dravet *et al.* 2002). Prolonged febrile seizures occur during the first year of life; they can occur in clusters in the course of one day, and often after vaccinations. Later, these seizures occur without fever, and at the same time a slowing of psychomotor development becomes manifest. The seizures are mostly myoclonic between the ages of one and five years, atypical absences between the ages of one and three years, and focal seizures between the ages of 15 and 36 months. Tonic seizures are rare. Status epilepticus takes the form of generalized tonic-clonic seizures, atypical absences, partial seizures and, rarely, tonic seizures. Generalized seizures resemble the generalized seizures seen in idiopathic epilepsies: short duration with a short tonic phase. Seizures affecting one hemibody usually occur in young children between 16 months and three years. There are also falsely generalized seizures with asymmetric bilateral tonic contraction leading to different postures during the seizure.

Unstable seizures are characterized by a topographic change in clinical discharge in the course of the same seizure. All seizures can also take the form of status epilepticus. Photosensitivity and hyperthermia are predisposing factors. Initially, the EEG during the first year of life is most often normal. In the course of evolution, the EEG becomes pathologic, with the appearance of focal, multifocal, and generalized discharges on a slow background activity. Photosensitivity is not constant but may occur as early as three months. MRI is normal, showing at most moderate cerebral atrophy. Long-term evolution is unfavourable, with intellectual deficit and ataxia, and hyperkinetic behaviour. Sensitivity to fever persists throughout life. Treatment of seizures remains difficult and the most effective anti-epileptic therapy is still stiripentol in combination with Valproate and benzodiazepines, particularly clobazam. Topiramate seems to be a promising anti-epileptic drug.

Myoclonic astatic epilepsy

Formerly called Doose's syndrome (described for the first time by Doose *et al.* 1970), this syndrome is characterized by the occurrence in normal children aged 18 and 60 months (peak at 36 months), of generalized seizures of a myoclonic or a myoclonic astatic nature (100% of cases), leading to recurrent falls. The EEG shows generalized spikes. There is associated cognitive deterioration. The other manifestations observed include absences (60 to 90%) with high incidence of non convulsive status, tonic-clonic seizures (75 to 95%). Tonic seizures can also occur in this context (30 to 95%).

Genetic factors are often involved. In 10 to 30% of cases, febrile convulsions are noted. The EEG tracing shows monomorphic centroparietal theta activity with possible myoclonic status characterized by generalized complexes of 2-3 Hz polyspike waves. Myoclonic-astatic syndrome and Lennox-Gastaut syndrome have in common the same age at onset, the same generalized seizures causing falls, and psychomotor delay. But in contrast to most Lennox syndromes, there is no underlying lesion and there is often a history of familial epilepsy.

The most effective treatment is valproate alone or in combination with lamotrigine, and benzodiazepines. Carbamazepine and vigabatrin are contraindicated due to a considerable risk of aggravation of the syndrome (Guerrini *et al.* 2002).

Conclusion

When faced with psychomotor delay, the role of epilepsy must be determined: is it involved in the cognitive deficit? Is it spontaneous? Is it the consequence of an underlying neurological lesion? In this context, a series of clinical, electrophysiological and neuroradiology investigations; as well as knowledge of the relation between age and the epileptic syndromes, are mandatory. □

References

Aicardi J, Baraton JA. Pneumo-encephalographic demonstration of brain atrophy following status epilepticus. *Dev Med Child Neurol* 1971; 16: 660-7.

Castroviejo I, Diaz-Gonzalez C. Sturge-Weber syndrome: study of 40 patients. *Paediat Neurol* 1993; 9: 283-8.

Chauvel P, Dravet C. In: Roger J, Bureau M, Dravet C, Genton P, Tassinari CA, Wolf P, eds. *Le syndrome HHE (Hémiconvulsion-Hémiplégie-Epilepsie)*. Eastleigh: John Libbey Eurotext, 2002: 247-63.

Coley SC, Britton J, Clarke A. Status Epilepticus and venous infarction in Sturge-Weber syndrome. *Childs Nerv Syst* 1998; 14: 693-6.

Curatolo P, Veredecchia M, Bombardieri R. Tuberous sclerosis complex: a review of neurological aspects. *Eur J Pediatr Neurol* 2002; 6: 15-23.

Doose H, Gerken H, Leonhardt R, Voelzke E, Voelz C. Centrencephalic myoclonic-astatic petit mal. Clinical and genetic investigations. *Neuropediatrie* 1970; 2: 59-78.

Dravet C, Bureau M, Oguni H, Fukuyama Y, Cokar O. In: Roger J, Bureau M, Dravet C, Genton P, Tassinari CA, Wolf P, eds. *L'épilepsie myoclonique sévère du nourrisson (syndrome de Dravet)*. Eastleigh: John Libbey Eurotext, 2002: 81-104.

Gaggero R, Devescovi R, Zaccone A, Ravera G. Epilepsy associated with infantile hemiparesis: predictor of long term evolution. *Brain Dev* 2001; 23: 12-7.

Gastaut H, Vigouroux M, Trevisan C, Regis H. Le syndrome hémiconvulsion-hémiplégie-epilepsie ou syndrome HHE. *Rev Neurol* 1957; 97: 37-52.

Guerrini R, Parmeggiani L, Kaminska A, Dulac O. In: Roger J, Bureau M, Dravet C, Genton P, Tassinari CA, Wolf P, eds. *L'épilepsie myoclono-astatique*. Eastleigh: John Libbey Eurotext, 2002: 105-12.

Hart S, Andermann F. In: Roger J, Bureau M, Dravet C, Genton P, Tassinari CA, Wolf P, eds. *Le syndrome de Rasmussen*. Eastleigh: John Libbey Eurotext, 2002: 495-512.

Hennel SJ, Ekert PG, Volpe JJ, Inder TE. Insights into the pathogenesis of cerebral lesions in Incontinentia Pigmenti. *Pediatr Neurol* 2003; 29: 148-50.

Okumura A, Watanabe K, Negoro T, *et al.* MRI findings in patients with symptomatic localization-related epilepsies beginning in infancy and early childhood. *Seizure* 2000; 9: 566-71.

Senbil N, Sonel B, Faruk Aydin O, Kemal Y. Epileptic and non epileptic cerebral palsy: EEG and cranial imaging findings. *Brain Dev* 2002; 24: 166-9.

Ville D, Enjolras O, Chiron C, Dulac O. Prophylactic antiepileptic treatment in Sturge-Weber disease. *Seizure* 2002; 11: 145-50.