Clinical features and ethical issues in pediatric epilepsy

Caratteristiche cliniche e problematiche etiche nelle epilessie dell’età pediatrica

CARMEN BARBA
Pediatric Neurology, Children’s Hospital Meyer, Florence, Italy

Worldwide, fifty million people have epilepsy and around 85% of them live in developing countries. In particular, 25% of the global population with epilepsy is younger than 15 years of age. Prognosis in children with epilepsy varies from benign epilepsies in which remission occurs after a few years and treatment can often be avoided, to patients with drug-resistant seizures, which may require polytherapy and even surgical treatment. Due to the wide range of causes of epileptic syndromes, the possible negative psychosocial and cognitive consequences of seizures and the impact on quality of life, the management of children with epilepsy raises some relevant ethical issues: communication of diagnosis, the decision of starting a treatment after the first seizure, the use of new drugs in children and diagnostic challenges. Although surgery represents a viable therapeutic option for children with refractory focal epilepsy, the widespread use of surgical intervention must be regulated by evidence-based outcomes, pragmatism, and ethical principles. The cooperative work of neurologists, psychologists, caregivers and teachers can help face the challenges related to epilepsy, including the persisting stigma.

Key words: Epilepsy, drug-resistance, communication, antiepileptic drugs

Si calcola che ci siano 50 milioni di persone affette da epilessia nel mondo, e l’85% vive in paesi in via di sviluppo. Inoltre, il 25% della popolazione globale con epilessia ha meno di 15 anni. La prognosi dell’epilessia nei bambini è molto eterogenea e può variare da forme idiopatiche ad andamento favorevole che spesso non richiedono terapia a forme farmacoresistenti che possono richiedere una politerapia e persino un trattamento chirurgico. Considerate l’ampia variabilità delle cause delle sindromi epilettiche e le possibili conseguenze negative delle crisi in ambito psicosociale e cognitivo, la gestione dei bambini con epilessia è associata a rilevanti problematiche etiche: la comunicazione della diagnosi, la decisione di iniziare un trattamento e l’uso dei nuovi farmaci antiepilettici oltre alle difficoltà di raggiungere una diagnosi eziologica. Sebbene la chirurgia rappresenti un’opzione chirurgica praticabile, l’uso diffuso della chirurgia deve essere regolato dai risultati basati sulla medicina delle evidenze, il pragmatismo e i principi etici. Il lavoro collaborativo di neurologi, psicologi, genitori e insegnanti può aiutare ad affrontare le difficoltà collegate all’epilessia, compreso lo stigma.

Parole chiave: Epilessia, farmacoresistenza, comunicazione, farmaci antiepilettici
Introduction

Worldwide, fifty million people have epilepsy and around 85% of them live in developing countries. In particular, 25% of the global population with epilepsy is younger than 15 years of age (Guerrini, 2006) and the cause and clinical spectrum of epilepsy are extremely wide-ranging in children (Forgren, 2004). People with epilepsy could lead normal lives if properly treated, but for most of them this is not the case (Shorvon and Farmer, 1988). Overall, epilepsy contributed more than seven million disability-adjusted life years (DALYs) (0.5%) to the global burden of disease in 2000 (Leonardi and Ustun, 2002).

Epilepsy is suspected when there is repetition of seizures. Up to the age of 15 years 1.0-1.7% of children will have at least one unprovoked seizure and the cumulative risk of recurrence is 42% at 8 years follow-up, with only 3% of all recurrences occurring after 5 years (Shinnar et al., 1996). Prognosis in children with epilepsy may vary from benign epilepsies in which remission occurs after a few years and treatment can often be avoided, to patients with drug-resistant seizures, which may require polytherapy and even surgical treatment. Early response to drugs (75-100% seizure reduction within the first 3 months of treatment) is a good predictor of long-term remission, irrespective of etiology (Sillanpaa, 2000). Idiopathic and presumed symptomatic epilepsies are three times as likely to achieve remission than symptomatic forms (Sillanpaa, 2000).

Epilepsy has various negative consequences, which involve many areas of the child’s life, and some of them are related to the stigma associated with epilepsy (Collings, 1990; Gil-Nagel et al., 2001). People with epilepsy are perceived as sexually deviant, antisocial, aggressive, potentially violent, mentally ill and unattractive (Bishop and Hermann, 2000). Indeed, children and adolescents with epilepsy do have a high incidence of psychiatric, psychological and behavioural difficulties (Batzel et al., 1991). Psychiatric disorders are four times more frequent in children with epilepsy than in general population (Austin, 2001). Anxiety, depression and concomitant social withdrawal are highly prevalent in these children (Bax, 1999). Younger children with epilepsy show more hyperactivity/attention deficit and sociability problems, while older pediatric patients more often exhibit depression and anxiety (Sabbagh et al., 2006). Children with epilepsy exhibit feelings of embarrassment, frustration and helplessness and often, also dependence and demanding behaviour (Hoare and Kerley, 1991). Long-term follow-up studies of children with epilepsy showed an increased risk of unemployment, a significant possibility of completing only six or fewer years of school, social isolation, financial dependence, and less likelihood of getting married than a matched control sample (Guberman and Bruni, 1999).

School performance can be compromised in children with epilepsy, in particular in case of drug-resistant seizures (Aldenkamp et al., 2005). Children with uncontrolled seizures are at increased risk for missing classes with subsequent decline in school performance (Aguiar et al., 2007). Poor school performance has been associated with psychopathology in the caregiver, perceived stigma of having epilepsy and duration of the diagnosis of epilepsy (Adewuya et al., 2006). Also, teachers’ knowledge about and attitudes toward epilepsy can have a direct impact on students with epilepsy in terms of school performance, social skill development, and post-school achievements in the areas of employment and social adaptation (Hsieh and Chiu, 2001). A survey amongst 512 elementary and middle school teachers in the United States demonstrated that although teacher’s attitudes about epilepsy were generally positive, there were significant deficits in terms of general knowledge about epilepsy, its impact in educational settings, and the appropriate management of seizures in the classroom (Bishop and Boag, 2006).

Epilepsy and epileptic seizures

Epilepsy (Fisher et al., 2005) is defined as: ‘a disorder characterized by an enduring predisposition to generate epileptic seizures and by neurobiological, cognitive, psychological and social consequences of this condition. The definition requires the occurrence of at least one epileptic seizure’. Therefore, epilepsy is defined in practice as ‘two or more unprovoked seizures occurring at least 24 hours apart’ (Commission ILAE, 1993).

Active epilepsy indicates a person who is either currently being treated for epilepsy or whose most recent seizure has occurred within a time interval usually defined as the past 2 or 5 years (Commission ILAE, 2011). Epileptic seizure is defined as ‘a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain’ (Fisher et al., 2005). Epileptic seizures, even if recurrent, are not always synonymous with epilepsy per se. The following conditions are generally not considered to be related to epilepsy: (1) isolated unprovoked epileptic seizures, or a single cluster occurring within a 24-hour period or as a single episode of status epilepticus (SE); (2) febrile seizures or neonatal seizures (occurring in infants less than 28 days of age); (3) seizures in close temporal association with an acute systemic, metabolic or toxic insult or in association with an acute central nervous system (CNS) insult (infection, stroke, cranial trauma, intracerebral haemorrhage, or acute alcohol intoxication or withdrawal). Seizures due to such acute and transient conditions are also defined as provoked or acute symptomatic epileptic seizures.

In 1989 the ILAE Commission on Classification and Terminology introduced the concept of “epileptic syndrome” i.e. a group of signs and symptoms customarily occurring in association, including seizure types, clinical background, neurophysiological and neuroimaging findings and, often,
outcome. The 1989 Classification distinguished epilepsies in generalized and partial (or focal). Generalized epilepsies were defined as characterized by generalized seizures, bilateral motor manifestations, and generalized interictal and ictal EEG discharges. Partial epilepsies were characterized by seizures originating from a circumscribed brain region, and by clinical manifestations consistent with a focal onset of the epileptic discharge, with or without subsequent spread, and by focal ictal or interictal EEG abnormalities. The 1989 Classification divided the epilepsies by aetiology in: idiopathic, symptomatic and cryptogenetic. Idiopathic epilepsies were defined by absence of any brain lesions, normal background EEG activity and interictal generalized spike and wave discharges. They were considered to be due to a genetic predisposition or to a specific mode of inheritance. Symptomatic epilepsies were considered the expression of a focal or diffuse brain lesion as demonstrated by clinical history, structural neuroimaging, EEG findings, or biological tests. Cryptogenic epilepsies were defined as conditions of presumed symptomatic nature in which the cause has not been identified. The number of cryptogenic cases is diminishing, but they account for at least 40% of adult-onset cases of epilepsy. Since 1989, various attempts of revision of the Classification system have been made. A number of concept categories had been recognized and updated in the 2001 and 2006 ILAE Task Force reports and had been reinforced over time. For example, the term ‘cryptogenic’ had been discouraged since 2001 (Engel et al., 2001). On the other hand, the main syndrome categories introduced in 1989 still appear reliable for clinical and epidemiological purposes.

**Epilepsy surgery in children**

Only 5-10% of all incidence cases of epilepsy ultimately result in truly intractable disease. Approximately 60% of patients with intractable epilepsy can be expected to suffer from partial seizures. Failure to control seizures with the first or second AED implies that the probability of subsequent seizure control with further AEDs is only about 4% (Kwan and Sander, 2004). Approximately 5% per year of patients with intractable epilepsy are seizure free for 12 months following medication changes. Irrespective of the number of previous AEDs, there is hardly any possibility of inducing seizure remission in patients with pharmacoresistant epilepsy (Kerran and Riekkinen, 1993; Luciano and Shorvon, 2007).

The primary surgical aim of epilepsy surgery is the control of seizures rather than the removal of underlying lesion causing seizures, although in some cases epilepsy and its cause may deserve equal surgical attention. Since up to a third of patients with epilepsy do not respond to medication, surgery represents a viable therapeutic option for people with refractory focal epilepsy.

Children with seizures that are uncontrolled by medical treatment or are disabling (including medication side effects) are possible surgical candidates, in particular if there is evidence of lateralized seizures or of EEG focal activity or in whom brain MRI reveals a lesion amenable to surgical removal.

Developmental arrest or progressive disturbances in cognitive function, behaviour, and psychiatric state are common in pediatric epilepsy surgery patients and a consensus has been reached among the experts that early surgical intervention is critical in infants with severe epilepsy to prevent developmental arrest/regression (Cross et al., 2006). In 1970 years, Falconer introduced surgery as a feasible treatment of pediatric epilepsy and was convinced that early intervention could give children refractory to medical treatment a significant improvement in developmental outcome (Falconer, 1972). Negative outcomes in terms of a decline in cognitive, behavioural and neuropsychiatric functions are observed in pediatric epilepsy surgery patients and can influence the decision for surgical management. Even if the primary goal of surgery in children is to achieve seizure control, there is the potential for the added benefit of improved neurodevelopment (Cross et al., 2006).

A favourable seizure outcome after surgery does not guarantee improved behavioural or cognitive status; however, early surgical intervention may be critical in infants with catastrophic epilepsy to prevent developmental arrest/regression (Freitag and Tuxhorn, 2005).

Seizure freedom is strictly related to the possibility to remove the seizure onset zone. To identify the seizure onset zone it is then crucial to perform a presurgical evaluation protocol including prolonged video-EEG recording of ictal events, structural neuroimaging for identifying pathology causative of epilepsy, neuropsychological assessment and functional imaging (PET, fMRI, SPET). When localizing data from conventional methods do not allow us to generate a hypothesis about seizure onset zone, patients may undergo invasive recordings (Jayakar et al., 2014).

Surgical syndromes and etiologies are more diverse in children than in adults and recognized etiologies and syndromes more common in children include the followings (Cross et al., 2006; Obeid et al., 2009a and b).

**a) Cortical dysplasia**

Cortical dysplasia is the most common neuropathology substrate in pediatric epilepsy surgery and can be focal or multifocal. The lesion is not always apparent on magnetic resonance imaging (MRI), or the visible lesion may be only a small part of a diffuse structural abnormality. Complete resection of the entire lesion is associated with the best post-surgery seizure control.

**b) Tuberous sclerosis**

Children with tuberous sclerosis may have a single epileptogenic region suitable for resection despite having multiple
other tubers or multifocal/diffuse interictal EEG findings. Multiple epileptogenic regions pose a greater challenge in the evaluation process and a role may exist for multistaged resective procedures.

c) Hemispheric syndromes

Focal epilepsy in childhood may be associated with congenital pathologic conditions affecting an entire cerebral hemisphere, i.e. hemimegalencephaly and hemispheric dysplasia. Hemispherectomy or other hemispherotomy techniques are used to treat epilepsy associated with hemispheric syndromes with satisfying results.

Hemispherectomy or hemispheric disconnection represent also a viable treatment in Rasmussen syndrome which is characterized by the development of refractory partial seizures and progressive hemiparesis with radiological changes of slowly progressive hemispheric atrophy. Cognitive impairment is also apparent. The decision to perform surgery is often challenging, as the risk–benefit assessment requires considerable clinical experience, particularly when the dominant hemisphere is affected.

d) Mesial Temporal Syndrome (MTS)

MTS consists of seizures originating from the mesial temporal structures, with hippocampal sclerosis as their pathologic substrate. In surgical series most patients with intractable temporal lobe epilepsy have evidence of hippocampal sclerosis. Characteristic seizure semiology includes epigastric or psychic auras, followed by decreased behavioural activity or staring, slowly progressive clouding of consciousness, oro-alimentary and gestural automatisms. Seizure outcome after mesial temporal resection is considered as the most favourable among all surgically remidiable epilepsies.

Long-term effect of epilepsy on cognitive and psychosocial outcome

The course of normal development in childhood is largely affected by epilepsy. The onset of seizures pose children at higher risk for cognitive, behavioural and psychosocial impairment, compared to healthy population (see Blume and Parrent 2006 for a review). The prognosis of childhood epilepsy is strictly linked to intractability defined as a failure in seizures control in spite of different medical treatment options.

A number of studies demonstrated the high incidence of developmental delay in patients who have early onset of epilepsy, high seizure frequency and severity, and chronic antiepileptic medication (Vasconcellos et al., 2001; Meador et al., 2002; Freitag and Tuxhorn, 2005). In particular, it has been suggested that age of onset, seizures frequency and etiology represent the strongest factors influencing cognitive and behavioral outcome (Bourgeois et al., 1983; Huttenlocher and Hapke, 1990; Vasconcellos et al., 2001). A population-based study of 337 children and young adults with normal intelligence and epilepsy found high proportions of negative psychosocial and achievement outcomes: school failure (34%), special education utilization (34%), mental health consultation (22%), unemployment (20%), social isolation (27%) and inadvertent pregnancy (12%) (Camfield et al., 1993). A prospective study of a population-based cohort with epilepsy childhood onset followed for more than 30 years demonstrated negative effects on social and educational outcomes even in patients with idiopathic epilepsy in remission without medication (Sillanpaa et al., 1998). Worse outcomes were found in remote symptomatic seizures (Sillanpaa, 1998).

From a different perspective, Selwa et al. (2003), retrospectively surveyed 34 subjects with refractory partial epilepsy not eligible for surgery treatment and found at a follow up of a mean of 4.4 years a remission rate of 15-21% with long-term medical treatment. The authors concluded that the long-term prognosis in patients with refractory partial epilepsy who are not surgical candidates may be more positive than might be generally expected in terms of seizure outcome, high proportion of employment and rated satisfactory quality of life. These results seem not in line with the majority of studies on long-term outcome of childhood epilepsy surgery but the study included children with a relatively high mean age at epilepsy onset, which was not so early to influence the course of global development. As pointed out by Freitag and Tuxhorn (2005), cognitive deterioration may take place in a subset of patients who have early onset and long duration of epilepsy, suggesting a window of vulnerability for irreversible decline of cognitive potential. On these basis: a) better psychosocial outcomes would be expected for onset of seizures out of the window of vulnerability and b) worse cognitive and psychosocial outcomes would be expected when surgery is performed too late, beyond the window of vulnerability in which seizures started.

Cognitive outcome in relation to epilepsy syndromes

The study of long-term outcomes of separate epilepsy syndromes would be more clinically useful than the determination of general proportions of reaching positive end points (i.e. employment) in the life course of all pediatric epileptic patients (Engel, 2001). Nevertheless, our knowledge of the cognitive and behavioural impairments in childhood epilepsy and, most important, of the differential neuropsychological profiles associated to separate syndromes remains still very limited.

Children with partial epilepsy are more likely to present with specific cognitive impairments than children with generalized idiopathic epilepsy (Jambaque 1993; Bell et al., 2001; Pavone et al., 2001). When compared to controls, children with temporal lobe epilepsy show memory impairments cor-
related to the involved cortical hemisphere (Cohen et al., 1992; Jambaque et al., 1993). However, memory deficits have been reported also in children with extratemporal epilepsy (Jambaque, 1993) with no differences related to laterality and localization of seizures onset zone (Lendt et al., 1999; Smith et al., 2002).

The extent of the lesion is predictive of preoperative development and children with multilobar lesions are more likely to have a lower global cognitive level compared to children with lesions localized to the frontal or temporal lobe (Freitag and Tuxhorn, 2005). Poorer performance is also expected in children with dual pathology (Freitag and Tuxhorn, 2005).

**Cognitive outcome after epilepsy surgery**

The great proportion of studies on postoperative cognitive outcome has focused on the effects of temporal lobectomy and has largely excluded very young children and children with low intellectual level.

An association between preoperative low intellectual functioning and postoperative cognitive decline was reported by Lieb et al. (1982) and Rausch (1991). These results were explained in terms of the reduced ability to compensate for possible deficits after surgery due to diffuse brain pathology (Rausch 1991). However, Bjornaes et al. (2004) showed no deterioration in cognitive functioning or psychosocial adjustment in a sample of 31 patients, eight of which children, with intractable focal epilepsy and low IQ (≤ 70) undergoing temporal lobe or extratemporal resection. Freitag and Tuxhorn (2005) observed improvement in intellectual functioning in most children with low preoperative IQs/DQs. These authors hypothesized that global cognitive gains might indicate re-start of development after a period of arrest or regression due to severe epilepsy.

Loddenkemper et al. (2007) preoperatively and postoperatively assessed 24 infants (median age at surgery=14 months; 14 hemispherectomies and 10 focal resections) using a standard protocol including the Bayley Scales (1969). The developmental quotient improved in 71% of infants, whereas postoperative DQ declined in 7 children. Better outcomes were observed in patients with epileptic spasms operated at a younger age. Global developmental gains may require a longer period after surgery to become statistically significant and clinically relevant.

Normal global cognitive development after childhood epilepsy surgery can also be observed in the context of early onset memory deficits as a result of bilateral hippocampal lesions, in spite of severe deficits in everyday functioning and episodic memory (Vargha-Khadem et al., 2001).

Some studies on memory outcome after temporal lobe surgery in children observed a decline (Dlugos et al., 1999) while others did not report any significant change (Lendt et al., 1999). As suggested by Gleissner et al. (2005), compared with adults, children may be less vulnerable to memory decline after surgery. Children also evidenced an improvement on attentional functions one year after surgery (Gleissner et al., 2005).

The impact of epilepsy surgery has been also measured in terms of impact on motor performance, activities of daily living and caregiver assistance. Van Empelen et al. (2005) showed that 2 years after surgery (which included hemispherectomies, temporal and extratemporal resections, and callosotomy) the motor function of most children with and without spasticity followed the expected development; independence in daily live activities increased thus reducing the need for caregiver assistance.

Quality of life seems to be strictly linked to clinical outcomes. After temporal lobe surgery, health-related quality of life improves or remains stable in seizure-free patients despite memory decline, but a worse quality of life has been observed when persistent seizures are accompanied by memory decline. In patients who experienced extended seizure remission for at least 2 of the 5 years of follow-up, quality of life improved, regardless of whether memory had declined (Langfitt et al., 2007). Parents of children who received hemispherectomy reported similar levels of health-related quality of life compared to nonsurgical patients. However, in surgical patients, residual seizure frequency, antiepileptic drug load, and lower functional abilities, appear particularly detrimental to life quality in pediatric epilepsy (Griffiths et al., 2007).

The few neuropsychological studies in children who underwent focal extra-temporal resections have found greater preoperative cognitive impairment compared to temporal lobe patients, smaller likelihood of cognitive improvements and higher frequency of individual cognitive declines (Helmstaedter and Lendt, 2001; Lah et al., 2004).

The lack of conclusive evidence about postoperative cognitive outcome in children is related to the methodological flaws of most studies (i.e. small sample size, few neuropsychological test, and very different mean age at surgery). The lack of control groups is the most common weakness of epilepsy surgery studies (Engel et al., 2003) and this is particularly true for children and adolescent populations. In many studies, controls were children not eligible for surgery, in others they were adults, and some studies did not describe controls characteristics. Sample size varied substantially among studies, but was in general small: less than 20 patients per group.

**Ethical issues in epilepsy**

Due to the wide range of causes of epileptic syndromes, the possible negative psychosocial and cognitive consequences of epilepsy and the impact on quality of life, the management of children with epilepsy raises some relevant ethical issues that we will address in the next paragraphs.
Communication of the diagnosis: It is important to communicate the diagnosis to both parents using a calm approach and in a restful environment. The referral neurologist should precisely explain what seizures and epilepsy might represent in the life of child. The characteristics of the epileptic syndrome should be described in lay terms and all questions by the parents should be answered as specifically as possible. It is crucial to try to define the possible prognosis in terms of seizure control and cognitive consequences. If additional investigations are needed to get the correct diagnosis, parents should be aware of the risks and benefits related to the diagnostic tests suggested. Parents should be trained about the management of seizures at home i.e. for the administration of rescue treatment and the safe management of the child during the ictal event. Parents should also be helped to solve the possible adjustment problems at school.

Starting a treatment after the first seizure: In case an antiepileptic drug is needed, risks and benefits of the medical treatment should be elucidated. Potential risks of having recurrent seizures, on and off medication, need to be discussed with the parents. Whether to treat a single unprovoked epileptic seizure becomes an individual decision for each patient, dependent from the possible detrimental effect of AEDs on one hand and the risks and consequences of a second seizure on the other. At some point, drug discontinuation must be considered and the parents (and the patient in case of older children) must be involved in the decision.

Use of new drugs: For children who do not respond well to treatment, the clinical goal is to find an optimal balance between the benefits and side effects of any medical treatment. For the newly, or recently, diagnosed population, the key question for the newer drugs is how soon they should be tried. The cost-effectiveness of using these agents early, in place of one of the older agents, will depend on their effectiveness and tolerability compared with the older drugs. The evidence from the available trial data suggests that the newer agents are no more effective but may be better tolerated than the older agents, and so the cost-effectiveness for early use will depend on the balance between effectiveness and tolerability. There are insufficient data available to estimate accurately the nature of this trade-off either in terms of long-term treatment retention or utility (Connock et al., 2006). While waiting randomized clinical trials specifically designed for the pediatric age, the use of newer agents should be limited to children resistant to older drugs and who developed unacceptable collateral effects. Furthermore, risks and benefits of the use of newer drugs should be precisely explained to the parents in order to sign a consent form. Subsequently, children should be followed at short term to allow the detection of collateral effects, if any.

School and relationship with teachers: The relevant role of teachers in the management of children with epilepsy has been challenged by a number of historically problematic and stigmatizing ideas about epilepsy and persons with epilepsy. It is crucial to pay attention to the potentially critical role that teachers play in the relationship between the early educational experience and future quality of life, also because a significant number of teachers feel unprepared to effectively deal with a number of aspects of epilepsy. To solve these issues it would be important to identify ways to increase exposure to accurate epilepsy information and provide information about appropriately handling seizures in the educational setting and to increase awareness of and access to existing educational resources, such as through the patient associations.

Genetics and epilepsy: Genetic testing, when positive, can provide patients with prognostic and diagnostic information. Nevertheless, in some common epilepsies, the role played by genetic testing cannot be clearly established even if a gene or locus has been identified. Establishing a link between abnormalities or common polymorphisms and manifestation of disease or drug resistance will be a major challenge (Goddard and Cardinali, 2004). Genetic counselling aims to inform individuals and families who are concerned about a genetic disorder. The daunting challenge is to be sure that people clearly understand the role played by heredity and genetics, which can easily be misinterpreted by laypersons, in particular in cases of polygenic and multifactorial disorders such as epilepsies. Thus, genetic counselling for epilepsies should include:

a) an assessment of the patient risk perceptions and expectations;
b) the interpretation of the test, including its sensitivity and specificity and the probability of obtaining a positive, negative, or nonconclusive result;
c) a description of the methods used to obtain blood samples. When DNA samples have to be obtained from family members to perform an informative genetic test, the issue of privacy must be taken into account;
d) a plan for the communication of results to the family and patient, in case of older children. In case of preventable or treatable conditions, it may be important for family members to be informed of their own risk.

Ethical issues in epilepsy surgery

Surgery with curative or palliative intent entails cortical resection, functional disconnection, or neuromodulation. Epilepsy surgery in the pediatric population has gained popularity owing to surgically amenable seizure etiologies in children, toxicity of antiepileptic medication on the developing brain, and functional plasticity at younger ages. Surgical treatment can result in greater reduction in seizure frequency compared to medical therapy and is considered a cost-effective treatment option in children with intractable epilepsy. The widespread use of surgical intervention for medically intractable epilepsy must, however, be regulated by evidence-based outcomes, pragmatism, and ethical principles.
Delay in surgical treatment: Only a minority of younger children with seizures who are at greatest risk of negative cognitive consequences receive surgery within 2 years of seizure onset (Devlin et al., 2003; Cross et al., 2006; Delalande et al., 2007). This delay seems to be related to a conservative attitude in the clinical approach to medical intractability, which can shift for too long the opportunity to treat epilepsy with surgery. The strategy of trying all antiepileptic drugs would take, in terms of pharmacological treatment plan, many years. Excessive delay could reduce the efficacy of surgery treatment thus leaving unchanged the natural history of resistant epilepsy and increasing the risk for unfavourable consequences in long-term physical and psychosocial health. These issues become particularly important for early onset of uncontrolled seizures and for the associated deleterious effect to the developing brain (Cross et al., 2006). Early onset of epilepsy and high seizure frequency and severity may influence cognitive and behavioural outcome (Freitag and Tuxhorn, 2005; Vasconcellos et al., 2001, Meador et al., 2002) reducing the developmental potential in children. On the other hand, the child's brain is capable of significant reorganization of neurologic function after insult and surgery, a unique and complex phenomenon that is critical for surgical planning (Cross et al., 2006). Neural plasticity issues are of primary importance to surgical management, as the possibility of removing eloquent cortex next to epileptogenic lesions permits more complete procedures with potentially higher rates of success. Surgical planning for associated epilepsy should therefore be based on individual assessments of structural imaging and of the relationship with eloquent regions (Guerrini et al., 2008). Finally, although brain plasticity can facilitate neurologic reorganization after treatment, it may also act as a negative influence in that early-onset epilepsy and may trigger deviant or delayed development (Cross et al., 2006).

As an additional relevant issue, we have no empirical data concerning the impact of specific neuropsychological disturbances, caused by surgical treatment itself, on the expected developmental curve, whereas different studies have widely demonstrated how that curve shifts from normal development in childhood resistant epilepsy. As reported in a recent review, after epilepsy surgery a decline in specific cognitive and functional principles.

Informed consent: There are three conditions that must be met when obtaining informed consent: (1) full disclosure, (2) lack of undue influence, and (3) a capable patient. The most common challenge faced in obtaining informed consent from children is related to their capacity to understand risks and benefits of the surgical treatment. Traditional perceptions of children as being prerational and premoral have been largely discredited by a large body of evidence demonstrating children's maturity and understanding of illness (Alderson et al., 2006). Experience, rather than age or ability, determines child's competence (Alderson et al., 2006). Therefore, when possible, a general assent is generally obtained from young children or those with cognitive delay. Instead, caregivers provide consent on behalf of children.

In cases of life-threatening illness, the child’s best interest would be to undergo surgical intervention. For epilepsy surgery however, apart from status epilepticus, the concept of best interest can be more difficult to define (Diekema, 2004). For instance, some families may prefer surgical treatment even if epilepsy is well controlled on monotherapy as they are aware of the collateral effects of medication and would like to offer to their child the possibility to become seizure-free and withdraw AEDs. The decision to perform epilepsy surgery can be more difficult if surgical treatment includes the resection of functional cortex or of an area close to functional areas, which might result in possible postoperative neurological deficit. For example, the resection of seizure onset zone within Rolandic cortex can result in postoperative hemiparesis (Benifha et al., 2009; De Oliveira et al., 2011). Patients or proxy decision makers may choose to sacrifice eloquent brain for becoming seizure free. An argument favouring resections of eloquent cortex is based on four premises: (1) children with drug-resistant epilepsy suffer as a result of their condition; (2) epilepsy surgery is likely to obtain seizure freedom; (3) seizure freedom cannot be obtained using less invasive approaches and (4) is worth the risk of surgery. The thresholds for epilepsy surgery in children may therefore depend on multiple factors including seizure etiology, proposed surgical strategy, the family's psychosocial dynamic and the child's clinical features.

Recognition of ethical challenges frequently encountered in the management of medically intractable epilepsy is central to providing responsible, patient-centered care to children.

New techniques in epilepsy surgery setting: At present, there are no accepted guidelines to support the surgeon in evaluating surgical innovations and ethically applying them to patient care. Innovations in seizure-localization represent a step towards the improvement of the quality of life of children with epilepsy. However, the use of innovative tools must be guided by evidence-based outcomes, pragmatism and ethical principles.

AED withdrawal after surgery: Long-term treatment itself can have an impact on cognitive and behavioural functioning, since most drug-resistant patients are in polytherapy. Despite the main specificities of pediatric epilepsies related to brain development, usually, treatment efficacy inferences are made extrapolating data from adults to children. Specific pharmacological trials on drug-resistant epilepsies are still not performed in children (Chiron et al., 2008). In this situation it’s hard to evaluate the cognitive impact of AED withdrawal.
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drival after successful surgery. Schiller et al (2000) found that in adults AED withdrawal was associated with seizure recurrence in a significant portion of patients and that the duration of seizure-free postoperative AED treatment interval did not significantly influence the seizure recurrence rate. However, a recent meta-analysis (Tellez-Zenteno et al., 2007) suggested that children achieved better AED outcomes than adults after surgery. Lachhwani et al (2008) assessed that in 97 children submitted to successful surgery, freedom from seizures 6 months after surgery predicted good outcome (95% seizure free, with or without medication). According to a recent retrospective study (Boshuisen et al., 2012) early AED withdrawal does not affect long-term seizure outcome or cure but might unmask incomplete surgical success. Moreover, the same authors assessed that AED withdrawal significantly improves IQ after childhood epilepsy surgery. Latest IQ scores and gain in IQ are both related to start of AED withdrawal, number of AEDs reduced, and to complete AED withdrawal, independently of other determinants of postoperative cognitive outcome (Boshuisen et al., in press).

Conclusions

Epilepsy in children raised many ethical issues, most of them are far from being solved. However, the cooperative work of neurologists, psychologists, caregivers and teachers can allow facing the challenges related to this condition, including the persisting stigma. Future studies including large cohorts of patients are needed in order to improve the yield of available diagnostic tools and develop new therapeutic options.

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