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New approaches to paediatric epilepsy

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ABSTRACT Clinical and basic research in paediatric epilepsy continues to have a direct impact on the diagnosis and treatment of children with seizures. In recent years, advances in molecular biology are beginning to unravel the molecular processes underlying childhood epilepsy, and there is increased understanding of the role of ion channels (and their interacting proteins) in the pathophysiology of epilepsy. Clinical trials and Cochrane reviews of diagnosis, treatment and outcome have also contributed to the management of paediatric epilepsy. This symposium provided an excellent forum for the presentation of such advances in the molecular pathogenesis, diagnosis and management of childhood epilepsies and related co-morbidities. Lectures were interspersed with interactive case presentations that illustrated contemporary approaches to paediatric epilepsy and allowed current controversies in this field to be debated.

KEYWORDS Antiepileptic drugs, epilepsy syndromes, ion channels, paediatric epilepsy, seizures

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INTRODUCTION

To improve outcomes for children with paediatric epilepsy there needs to be increased understanding of the aetiology and pathogenesis of these conditions, as well as more accurate diagnosis and appropriate therapeutic management strategies. This symposium successfully summarised new approaches in paediatric epilepsy. Lectures focused on epileptic syndromes of the newborn, infancy, childhood and adolescence (as well as their associated morbidities). Interactive workshops followed each lecture session focusing on cases which amplified the topics previously presented, allowing further detailed discussion of key principles in management.

SESSIONS 1 AND 2: NEONATAL SEIZURES

Dr Ronit Pressler (Consultant in Clinical Neurophysiology, Great Ormond Street Hospital, London) opened the symposium by discussing advances in the diagnosis and treatment of neonatal seizures. Seizures are more common in the neonatal period than at any other time throughout life (incidence 1–3/1,000 term infants). The incidence is ten times higher in preterm/low birth-weight infants.[1–3] Volpe's classification of neonatal seizures[4] includes subtle (the most common type), clonic, myoclonic and tonic events, whereas the classification by Mizrahi integrates subclinical seizures and information on the origin of events (epileptic and non-epileptic).[5] Aetiology is diverse,[6] but in term infants the most common cause of neonatal seizures is hypoxic-ischaemic injury, while in preterm infants, intracranial haemorrhage is the most frequent underlying factor. Rarely, neonatal seizures are due to syndromes such as benign idiopathic neonatal convulsions (fifth-day fits) and benign familial neonatal convulsions (associated with ion channel gene mutations, *KCNQ2* and *KCNQ3*).[7] The large differential diagnosis demands that initial investigation should focus on the more common aetiologies which require prompt and specific treatment.

There is an important but underrecognised role of electroencephalograms (EEG) to confirm clinical suspicion, diagnose subclinical electrographic seizures (in cases of electroclinical dissociation) and predict outcome. The role of cerebral function monitor (CFM) remains controversial, requiring skilled analysis of data for accurate interpretation. As neonatal seizures are ill-sustained and often focal, diagnosis can be difficult and may be made solely on clinical grounds.

The management of neonatal seizures remains controversial. Although there is some evidence that phenobarbitone may be an effective first-line anti-epileptic agent,[8] the current lack of clear, evidence-based guidelines in the treatment of neonatal seizures has resulted in diversity of clinical practice.[9,10] In addition, it has also been reported that although clinicians appear to make similar antiepileptic drug choices in the management of neonatal seizures (phenobarbitone first line, phenytoin second line and benzodiazepines third line),[9] there is wide clinical variability in the duration of drug treatment,[9,10] choice of drug in refractory neonatal seizures[9] and electrographic monitoring of seizures.[9] This variation in clinical practice may be partly due to the lack of clear evidence of the relative benefit and harm of anticonvulsants.[11] Additionally, both phenobarbitone and phenytoin can increase

electroclinical dissociation, which can make a clinical assessment of response to medication difficult.

Further elucidation of the pathophysiology of neonatal seizures may help resolve the management dilemma we currently face. Recently, blockade of the Na(+)-dependent K(+)-Cl(–)-cotransporter isoform 1 (NKCC1) has been found to have an important role in neuronal inhibition in the immature brain, and bumetanide (NKCC1 inhibitor) has been found to suppress epileptiform discharges in immature mouse models.[12] In the future, further elucidation of the pathogenesis of neonatal epilepsy may lead to the development of more effective targeted therapies. It is also clear that there is a pressing need for controlled clinical trials to establish evidence-based guidelines and protocols for diagnosing neonatal seizures, studying the efficacy and safety of antiepileptic agents (including the newer generation antiepileptic drugs in neonates) and determining optimum duration of drug administration.[13]

INFANTILE SEIZURES

Dr Elaine Hughes (Consultant Paediatric Neurologist, Evelina Children's Hospital and King's College, London) discussed the diagnosis and investigation of seizure syndromes presenting in the first year of life. Paroxysmal events in children may be epileptic or non-epileptic (such as syncopal events, behavioural phenomena, other neurological disorders, sleep myoclonus and gastro-oesophageal reflux). Epileptic syndromes of infancy may be benign (such as benign myoclonic epilepsy of infancy and benign familial infantile seizures) or more progressive in nature, such as Dravet, Ohtahara and West syndromes.[14]

West syndrome is the most common epileptic encephalopathy of infancy where epileptic spasms are associated with an abnormal EEG (classically hypsarrhythmic, but may be atypical) and developmental regression. It is due to a wide variety of structural, metabolic and genetic aetiologies. Currently, treatment of West syndrome is mainly independent of aetiology, and first-line agents include ACTH and vigabatrin[15] (except in tuberose sclerosis where there is some evidence that vigabatrin may be more effective).[16] From 2007, the International Collaborative Infantile Spasms Study (ICISS) group are conducting a four-year, multicentre, randomised controlled trial, comparing the use of steroid treatment in combination with vigabatrin to the use of hormonal treatment alone. Outcome measures include short-term effects on seizure control and long-term developmental progress. It is hoped that this trial will provide important information on the efficacy of current treatments used in clinical practice as well as delineating the disease course. It remains a mystery why such a narrow spectrum of antiepileptic agents is efficacious in infantile spasms, especially when there is a broad spectrum of underlying aetiologies. Future management of infantile spasms will certainly be influenced by elucidation of the pathogenetic mechanisms involved in West syndrome.

The management approach to paroxysmal events in infancy should include an accurate history, detailed clinical examination and, if possible, observation of home videos to distinguish epileptic from non-epileptic phenomena. An EEG (including a sleep recording) may then guide epilepsy syndrome diagnosis. Further investigations may include neuroimaging (MRI) as well as blood, cerebrospinal fluid (CSF) and urine neurometabolic investigations, genetic tests (if a specific phenotype is suspected) and an ophthalmological review, which may aid identification of an underlying diagnosis. In refractory infantile seizures, a trial of pyridoxine, pyridoxal phosphate, folinic acid or biotin (once a biotinidase level has been sent) may be warranted.[17,18]

SESSION 3 THE IDIOPATHIC EPILEPSIES

The idiopathic epilepsies represent a group of epileptic disorders where there are still multiple controversies regarding treatment. Dr Colin Ferrie (Consultant Paediatric Neurologist, Leeds General Infirmary) addressed these issues of when, if and how long to treat idiopathic epilepsies. An idiopathic epilepsy syndrome is defined as a syndrome that is only epilepsy, with no underlying structural brain lesion or other neurological signs or symptoms. These syndromes are presumed to be genetic and age-dependent. There are generalised idiopathic epilepsies (such as childhood absence epilepsy and juvenile myoclonic epilepsy) as well as focal idiopathic epilepsies (benign rolandic epilepsy, Panayiotopoulos syndrome). The decision to start antiepileptic drug (AED) treatment should be based upon knowledge of the risk of seizure recurrence (with and without treatment), the chances of adversely affecting the likelihood of long-term remission without treatment, the possibility of developing co-morbidities without treatment and the risk of dying without treatment.

Independent population-based studies[19,20] demonstrate that AEDs following an initial epileptic seizure significantly reduce the risk of further seizures. However, they also show that AEDs do not alter the disease course and probability of eventual seizure remission. In the majority of cases, omitting or postponing treatment after a solitary seizure, an unprovoked status epilepticus, a single burst of seizures or multiple infrequent seizures usually does not worsen prognosis.[21] Intellectual decline caused by seizures or epilepsy is generally considered to be rare and may be confined to certain specific and readily recognisable syndromes.[21] Idiopathic epilepsies may be associated with cognitive dysfunction and academic underachievement at the onset of seizures.[22] However, it remains unclear as to whether this is due to an antecedent cognitive impairment (due to an underlying

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neurological deficit) or the actual epileptic process. Idiopathic epilepsies are not associated with increased mortality.[23,24] Meta-analysis studies in children comparing early versus late withdrawal (two years' seizure freedom) of AEDs showed that the latter is associated with a lower risk of seizure relapse.[25]

Thus, three considerations might lead to the decision to start early and aggressive antiepileptic drug treatment: the dangers of the seizures, the chance of intractability and the possibility of intellectual decline caused by recurrent seizures or epileptic activity. A poor prognosis and the consequent indication for early and aggressive treatment are dependent mainly upon the presence of variables like symptomatic aetiology, certain epilepsy types and syndromes and the early evolution of the epilepsy in that particular child. In conclusion, the decision to start AEDs in children with idiopathic epilepsies should be based upon a consideration of their frequency, symptomatology and the likely immediate adverse effects of seizures, balanced against the risks of AEDs. Of note, for many children with idiopathic focal epilepsy syndromes, treatment is not required.

EPILEPSY CO-MORBIDITY: BEHAVIOURAL PROBLEMS

Dr Ailsa McLellan (Consultant Paediatric Neurologist, Royal Hospital for Sick Children, Edinburgh) presented a lecture on the prevalence and nature of behavioural problems in children with complex epilepsy, by defining the underlying aetiological mechanisms and illustrating a stepwise approach to the assessment and subsequent management of such disorders. Children with epilepsy are at significant risk of mental health problems (54% complicated epilepsy, 28% uncomplicated epilepsy) when compared with the general population (9%) or other children with non-neurological chronic disease (diabetic children 11%).[26] These mental health problems include conduct, emotional and pervasive developmental disorders, as well as attention deficit hyperactive disorder.

Factors contributing to behavioural problems include the stigmatisation and psychosocial burden of having a chronic illness as well as the underlying neurological condition and associated learning disability. The epilepsy itself may aggravate behaviour, especially in symptomatic generalised epilepsy, newly diagnosed epilepsy, epilepsy diagnosed at a young age or poorly controlled epilepsy. An epileptic seizure (such as a frontal, temporal or absence event) or the pre/postictal state may mimic behavioural problems. Severely abnormal EEGs (such as continuous spikes and waves during slow wave sleep, CSWS) may also manifest as behavioural abnormalities and may require treatment with AEDs.[21,27] Additionally, drug therapy may contribute to mental health issues, particularly certain antiepileptic drugs (such as sodium valproate), the use of polytherapy and poor drug compliance. Familial factors and life events may also add to the problem. A stepwise approach to the management of behavioural problems is advocated.[28] This involves initial accurate assessment and identification of the problem.

In cases of pervasive behaviour, reversible neurological issues and AED side effects should be addressed prior to a Child and Adolescent Mental Health Services (CAMHS) referral (if there are persistent behavioural issues). Situational behavioural issues should be dealt with at home with the support of the health visitor (under five years) and the CAMHS (over five years) and at school with the involvement of the educational psychologist and community paediatrician.

Future investigation of neurobehavioural difficulties associated with epilepsy may further define the nature of such co-morbidities. Large cohort studies may even delineate which forms of epilepsy predispose to certain behavioural phenotypes. Increased awareness of the impact of epilepsy on behaviour and cognition can thus lead to earlier recognition of neuropsychologcal problems, which is vital for the optimum management of such difficulties.

GENETICS AND EPILEPSY

It is becoming more evident that elucidation of the genetic basis of seizure disorders is increasingly contributing to the management of paediatric epilepsy.[29] Dr Sameer Zuberi (Consultant Paediatric Neurologist, Royal Hospital for Sick Children, Glasgow) provided a current overview of epilepsy genetics. Several hundred genetic disorders result in epilepsy as part of the neurological phenotype. Single gene defects can cause neuronal migration disorders, disorders of neuronal proliferation and disorders of integrity of the brain pial surface. Chromosomal disorders, such as deletions on chromosome 1 and 4 (Wolf-Hirschhorn) and ring chromosome 14 or 20 are also associated with epilepsy.

Chromosomal abnormalities may be due to duplications, deletions or breakpoint disruptions. In most epilepsies, it is likely that several genes contribute to the epileptic phenotype, possibly by acting synergistically to increase seizure threshold. Monogenic epilepsies are much rarer: to date, genes that have mainly been identified in large families (with multiple affected members) include those coding for neurotransmitter receptor components (such as GABA receptors) and ion channels. For example, Dravet's syndrome is a monogenic epilepsy with autosomal dominant inheritance where 70–80% of affected individuals have *de novo* mutations in the *SCN1A* gene,[30] coding for a voltage-gated sodium channel. This epileptic encephalopathy presents in the first year of life with prolonged hemi-clonic or generalised tonic-clonic seizures, progressing to multiple seizure types after the first year.[31] Genetic diagnosis in such children prevents unnecessary extensive neurometabolic investigations

and may guide therapeutic options, such as a trial of stiripentol.[32] Recent findings suggest that stiripentol acts as a direct allosteric modulator of the GABAA receptors (at a site distinct from many commonly used anti-convulsant, sedative and anxiolytic drugs), increasing inhibitory GABAergic transmission.[33] In summary, making a genetic diagnosis can help a family and clinicians understand the underlying cause of the epilepsy, and negates the need for extensive (and often invasive) neurological investigation. It may also help guide optimum drug therapy for the most favourable outcome.

CONCLUSIONS

This is an exciting time in the management of children with epilepsy, as new technologies and therapies begin to impact on patient care. As we begin to understand more about paediatric epilepsy, there will be improved diagnosis and management of our patients, allowing the ultimate goal of improved outcome to be realised.

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