NEUROLOGY

**G147** METABOLIC EFFECTS OF VALPROIC ACID IN CHILDREN UNDER 5 YEARS OLD

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**Aims:** Valproic acid (VPA) is an effective anti-epileptic drug in infancy, but is associated, rarely, with fatal hepatotoxicity. This study aimed to identify changes that were likely to be benign, and children developing hazardous toxicity.

**Methods:** 43 unselected children were studied before (28) or shortly after (15) starting VPA, 1 month and 3 months later. VPA was being used as a third line drug for epilepsy. Plasma VPA, urea, creatinine, albumin, liver enzymes, lactate, ammonia, free fatty acids, 3-hydroxybutyrate, glucose, free and total carnitine, quantitative plasma amino acids and urine organic acids and amino acids were analysed.

**Results:** 36% showed a rise in AST to >50 u/l after 3 months. 71% of those studied before VPA had ammonia concentrations within the reference range (<40 uM). Of these 57% showed moderate increases (40-90 uM) 1-3 months after starting. In 2 patients, ammonia rose to 99 and 124 uM with concurrent increases in lactate (5.9 and 4.5 mM respectively) with alkaline phosphatase (ALP) >1000 u/l. Cytochrome c oxidase deficiency was diagnosed in one; the other died unexpectedly with multiple congenital abnormalities, cause of death unknown.

**Conclusions:** The finding of elevated and rising plasma ammonia and lactate concentrations with elevated AST and ALP may predict a metabolic disorder likely to be compounded by VPA.

**G148** NEURODEVELOPMENT AND BEHAVIOUR IN THE FETAL ANTI-COAGULANT SYNDROMES

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Up to 1 in 200 pregnant women take anticoagulant medication for epilepsy, thus exposing the unborn child to a 5-10% risk of birth defect(s). Associated cognitive deficits and behavioural problems have been reported and there is much anecdotal experience for an increased risk of adverse neurodevelopmental outcome following in-uterine exposure to these drugs, these effects not necessarily being confined to those with a physical malformation. A study of 83 affected children from 54 assessed [exposed to valproate, carbamazepine, and phenytoin, alone or in combination] found a range of major and minor birth defects within the spectrum previously described, and the new feature of joint laxity (58%). Ophthalmic assessment in 46 subjects revealed a high incidence of myopia (35%) and astigmatism (24%). Learning difficulties occurred in 72%, speech delay 66%, hyperactivity or poor concentration 53%, and two or more autistic features occurred in 59%; 3 were diagnosed Asperger's and 6 autistic by a child psychologist. Gross motor delay was reported in 46% and fine motor delay in 42%. DNA analysis revealed a significantly increased frequency of the 677 C>T mutation in the maternal methylene tetrahydrofolic reductase gene compared to the affected children, their fathers, and a control group (Cin Gen 1996:58:216-220), supporting spec- ulation that genetically determinable variations in maternal folic acid metabolism predispose to risk of fetal anticoagulant syndrome.

Detailed controlled studies of cognition, behaviour and motor function in these children and adolescents are needed to clarify the risk of neurodevelopmental delay occurring in the offspring of women requiring anticoagulant medication in pregnancy.

**G149** EASY SLEEP WITH MELATONIN

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**Aim:** This study determined if melatonin can induce sleep reliably and safely.

Sleep induced by melatonin was compared to sleep induced by sleep depriva-
tion.

**Method:** Thirty children underwent a melatonin-induced sleep EEG. Depending on their age they were administered 2.5 or 5 mg of melatonin just before the EEG recording. Thirty of 50 children (matched for age and sex), who had a sleep deprived EEG in the same period, were used as the control group. Data was collected from the detailed request form, a parent questionnaire and a sleep diary and a telephone interview following the EEG. Differences between the two groups were analysed using the McNemar test (nominal scale) and Wilcoxon Signed Rank test (ordinal scale) with p < 0.05.

**Results:** No statistically significant difference was found between the 2 groups for age, sex, the prevalence of learning and behavioural difficulties. Sleep was obtained in 80% of the cases in both groups. The children in the melatonin group fell asleep within 21 minutes (+/- 2.2 95% CI). The sleep deprived group fell asleep within 34 minutes (+/- 7.9 95% CI). This was statistically significantly (p<0.013). Melatonin was acceptable and not associated with any adverse events.

**Conclusion:** Melatonin can induce sleep reliably in children undergoing EEG recordings. Melatonin is an attractive alternative to sleep deprivation for the induction of sleep EEG: it is safe, reliable and acceptable to patients. Melatonin could be used for other investigations requiring sleep.

**G150** A CLINICAL AND MOLECULAR GENETIC STUDY OF PATIENTS WITH COHEN SYNDROME

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Cohen syndrome, (CS), is an autosomal recessive cause of syndromic mental retardation associated with obesity, neutropenia, retinal dystrophy and a characteristic craniofacial appearance. Clinically, there is an overlap between CS and Prader-Willi and Bardet-Biedl syndromes. Delayed diagnosis is common, and reflects poor delineation of the phenotype as well as lack of a diag-
nostic test.

**Aims:** The study aims were to: (a) define the clinical phenotype in a UK cohort of CS patients; (b) determine whether genetic linkage exists to the locus identified in Finnish CS patients.

**Methods:** Patients were ascertained from Clinical Genetics Departments throughout the UK as well as via the CS Family Support Group. The family were interviewed by means of a detailed questionnaire. The patient was exam-
nined and blood taken to determine their neutrophil count. Molecular genetic analysis was performed using DNA samples from each family member.

**Results:** Of the 34 patients ascertained to date, 18 fulfilled the criteria decided upon for a firm diagnosis of CS. Their ages ranged from 3 to 46 years. Mean age at diagnosis was 10 years. Most patients had been floppy and fed poorly as babies. In all, their motor and speech development had been delayed. Most attended schools for moderate or severe learning difficulties. Adult patients lived at home and were not in employment. Most patients had a characteristic sociable personality. Dental infections were common problem in those with proven neutropenia. Visual problems included high myopia and poor night vision. 4/18 patients were registered as partially-sighted or blind by the age of 20 years.

**Conclusions:** Cohen syndrome in UK patients has a distinct clinical pheno-
type which shows linkage to the same genetic locus at 8q21-22 as identified in Finnish patients.

**G151** PROGRESSIVE INTELLIGENT AND NEUROLOGICAL DETERIORATION (PIND) IN CHILDREN

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**Aims:** To use the mechanism of the British Paediatric Surveillance Unit (BPSU) to identify all cases of progressive intellectual and neurological deter-
eriation (PIND) in children, particularly those with features suggestive of new variant Creutzfeldt-Jakob Disease (vCJD).

**Methods:** Using the BPSU report card, paediatricians are asked to report any child under 16 years of age at onset of symptoms who fulfils all of the following three criteria: progressive deterioration for more than three months with loss of already attained intellectual/developmental abilities and develop-
ment of abnormal neurological signs. Information is obtained via telephone interview or site visit. All cases are discussed by an Expert Neurological Advisory Group of seven paediatric neurologists which allocates them to a diagnostic category.

**Results:** After 29 months of surveillance, 773 children have been reported. 570 cases have been discussed by the Expert Group. Of these, 322 have been classified as PIND with a recognised cause. The top six reported conditions are the neuronal ceroid-lipofuscinoses (40 cases), the mitochondrial encephalo-
myelopathies (27 cases), GM2 gangliosidosis type I (Tay Sachs) (27 cases), metachromatic leukodystrophy (19 cases), adrenoleukodystrophy (16 cases) and Niemann Pick Type C (16 cases). 151 have yet to be allocated to a diagnostic group (pending further investigations and follow-up). 24 have been classified as idiopathic PIND (non-CJD). 220 have been classified as “No Case”. The remaining 56 cases are in the process of being followed up. So far, no definite case of vCJD has been identified but three suspected cases have been notified.

**Conclusions:** Surveillance for PIND is working satisfactorily, thanks to the active cooperation of UK paediatricians. The aim is to continue surveillance until at least May 2000.