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SEIZURE DISORDERS

CHILDHOOD OCCIPITAL EPILEPSY OF GASTAUT

The electroclinical features and evolution of childhood occipital epilepsy of Gastaut (COE-G) are analyzed in a study of 33 patients identified and followed between 1990 and 2007 at the Hospital National de Pediatria, Buenos Aires, Argentina. In comparison, over the same 16-year period, 201 children with Panayiotopoulos syndrome (PS) and 418 with benign childhood epilepsy with centrotemporal spikes (BCECTS) were registered. Age at onset of COE-G ranged from 4 to 16 years, with a mean of 8.5 yrs. Febrile seizures occurred in 5 patients (15%), migraine in 3 (9%), and BCECTS in 2 (6.5%). Family history was positive for epilepsy in 21%, febrile seizures (21%), and migraine (12%). Visual hallucinations were the initial seizure manifestation in 27 (82%). Blindness was the presenting symptom in 17 (52%) and the only clinical symptom in 5 patients. Postictal blindness and hemianopsia occurred in 7 patients (21%). Deviation of the eyes and ipsilateral turning of the head followed the visual hallucination in 20 patients (60%), and hemiconvulsions occurred in 45%. Eyelid closure and blinking occurred in 6 (18%). Migraine manifestations were prominent in 16 patients (48%). The duration of seizures was usually brief and <1-2 min. Seizures occurred while awake but sometimes in sleep. Frequency varied from 7 per week to one every 6 months. EEG showed occipital spike-wave paroxysms with eyes closed, disappearing with eyes open. All received antiepileptic treatment with valproic acid (15), carbamazepine (8), or oxcarbazepine (4). Seizures remitted within 2 to 7 years (mean, 4 yr) after onset in 80%, while EEG abnormalities persisted in 38%. AEDs were discontinued without relapse after 2-4 years in 54%. (Caraballo RH, Cersosimo RO, Fejerman N. Childhood occipital epilepsy of Gastaut: a study of 33 patients. **Epilepsia** Feb 2008;49(2):288-297). (Reprints: Dr Roberto H Caraballo, Department of Neurology, Hospital de Pediatria, Prof Dr Juan P Garrahan, Combate de los Pozos 1881, CP 1245,

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COMMENT. Childhood occipital epilepsy (COE) of Gastaut is manifested by brief seizures, mainly visual hallucinations, illusions or amaurosis, followed by hemiclonic seizures while awake, postictal migraine headaches, mean age at onset of 8.9 years, and interictal occipital spike-wave EEG paroxysms that attenuate when eyes are opened. Prevalence is estimated at 0.2-0.9% of epilepsies, and 2-7% of benign childhood focal seizures. Gastaut reported the syndrome in 1982, and it was accepted as an entity by the ILAE in 1989. Despite some recent loss of recognition, the present authors consider the syndrome as a rare but well-defined entity within the group of idiopathic simple partial (focal) epilepsies of childhood. Differential diagnoses include symptomatic occipital epilepsy, migraine with aura, and basilar migraine. Among the idiopathic COEs, the Gastaut type is of late onset and associated with visual symptoms, whereas Panayiotopoulos syndrome is of early onset and characterized by autonomic symptoms (ictal vomiting). The EEG findings alone are not diagnostic of COE. Not all children with occipital spikes develop seizures. Those with COE should be differentiated from patients with occipital spikes occurring both with eyes open and closed, and unassociated with clinical seizures. Occipital spikes also occur in children with myoclonic, absence, and photosensitive epilepsies. (Browne TR, Holmes GL Handbook of Epilepsy. Philadelphia. Lippincott, 2004;86-87).

RISK FACTORS FOR FEBRILE SEIZURE RECURRENCE

Factors that predict recurrence of febrile seizures (FS) were determined in a prospective study of 260 children age 3 months to 6 years followed for a median of 4.3 years after the first FS at Ippokratio Hospital, Aristotle University of Thessaloniki, Greece. The median age of patients at onset of study was 16.5 months (range 3 months to 5.8 years). Final reevaluation was at a median of 6.0 +/- 1.5 years. The sex ratio was 139 boys to 121 girls (1.15 : 1), and recurrence was not higher among boys than girls. Overall recurrence rate was 40.4%. Cumulative recurrence was 24.2% at 6 months, 34.2% at 12 months, 38.1% at 18 months, and 40.4% at 6 years. EEG abnormalities in 12 children at baseline were not significantly associated with FS recurrence. Low age at onset and positive family history of FS, especially maternal, were strong predictors of recurrence. Other risk factors included abnormal perinatal history with low Apgar score and NICU care for >3 days, low temperature (38.9C or below) and short (<12 hrs) duration of fever before initial FS, a history of frequent febrile illness ($p<0.0001$), focal FS, and recurrence within the same febrile illness. Duration >15 min of first FS was not a factor. Two or more recurrences occurred in 48%; 28 had only 2 and 22 (44%) had 3 or more recurrences. Factors predisposing a child with one recurrence to a second or more are young age at onset and family history of FS ($p<0.001$). Multiple recurrences were correlated with low temperature elevation (</=38.9C) before initial FS. By multivariate analysis significant risk factors were early age at onset, complex first FS, and family history of FS ($p<0.05$). (Pavlidou E, Tzitiridou M, Kontopoulos E, Panteliadis CP. Which factors determine febrile seizure recurrence? A prospective study. **Brain Dev** Jan 2008;30:7-13). (Respond: Dr Christos P Panteliadis, Department o Paediatric Neurology, Ippokratio Hospital, Aristotle University of Thessaloniki, Greece. E-mail: cpantel@hol.gr).

COMMENT. In confirmation of previous studies, the main predictors of susceptibility to febrile seizure recurrence are young age (<18 mo) at initial FS, family history of FS in first degree relative, lower temperature (</= 38.9C) and shorter fever duration (<12 hrs) before initial seizure. The lower temperature indicates a low threshold to FS. The present authors also found a maternal preponderance in the families of children with FS recurrence. Daycare attendance and frequent viral infection are additional risks.

Cytokines in acute encephalopathy following prolonged febrile seizures. In a study of 13 children with acute encephalopathy following prolonged febrile seizures compared to 23 without encephalopathy, in Yamaguchi University and other centers in Japan, serum IL-6, IL-10, TNFR1 and CSF IL-6 levels were significantly higher in subjects with encephalopathy compared to controls without encephalopathy. The authors speculate that IL-6 is induced in the CNS to protect damaged brain following prolonged febrile seizure.

PERTUSSIS VACCINATION, EPILEPSY AND *SCN1A* MUTATION

Literature regarding pertussis vaccination and risk of encephalopathy and/or epilepsy is reviewed by researchers from UCL Institute of Neurology, London, UK, and North Illinois University, DeKalb, IL, USA. Current risk estimates of vaccine-related febrile seizure are 1 per 18,496 vaccinations; afebrile seizure 1 per 76,133; and encephalopathy 0-3 per million. The rate of febrile seizures within 2 days of the present acellular vaccine is much lower than that of 1 per 2835 with previous whole-cell vaccine (Cody CL et al. Pediatrics 1981;68:650-660).

As part of a recent study of unexplained encephalopathies in Australia, New Zealand, Canada and Scotland, Berkovic SF et al (Lancet Neurol 2006;5:488-492) identified 14 cases within 72 hours of pertussis vaccination, treated by child neurologists. Of these presumed vaccine-related cases, 11 had an inherited genetic defect of the *SCN1A* gene that corresponded to the phenotype for severe myoclonic epilepsy of infancy (SMEI, Dravet syndrome). The encephalopathy temporally associated with pertussis vaccination may, in some cases, be due to an *SCN1A* mutation and Dravet syndrome. This finding requires replication by further studies. (Shorvon S, Berg A. Pertussis vaccination and epilepsy – an erratic history, new research and the mismatch between science and social policy. **Epilepsia** Feb 2008;49:219-225). (Respond: Dr Simon Shorvon, UCL Institute of Neurology, Box 5, National Hospital for Neurology and Neurosurgery, Queen Square, London, UK).

COMMENT. Fortunately, the risk of neurologic complications of pertussis vaccine has fallen remarkably since the introduction of the acellular vaccine. With whole-cell vaccine, reports of neurologic complications, especially febrile seizures or infantile spasms, were not uncommon in US pediatric neurology practice. In the same time period, encephalopathy attributed to whooping cough was a very rare neurologic diagnosis. In vaccine related encephalopathies, a test for SMEI should be considered in the differential diagnosis.

In Australia and New Zealand, the experience is different from the US. Among 49 unimmunized infants (age 6 weeks) admitted with pertussis to the PICU at Royal Children's Hospital, Melbourne, between 1985-2004, 63% had apnea, 18% pneumonia, and 10% had seizures. Deaths in 7 were due to pneumonia and circulatory failure. (Namachivayam P et al.

Pediatr Crit Care Med 2007;8:207-211). At Starship Children's Hospital, Auckland, NZ, 72 children (<12 months old) were admitted to the PICU with pertussis from 1991-2003. Apnea and cough were presenting symptoms in 83%, 4 died and 6 had neurodevelopmental problems. (Surridge J et al. **Arch Dis Child** 2007;92:970-975). In unimmunized populations, pertussis is a serious disease with complications, principally respiratory.

REVERSIBLE VALPROATE HEPATOTOXICITY AND ASSOCIATED MITOCHONDRIAL DISEASE

A 2-year-old boy with seizures complicated by reversible valproate-induced hepatic failure was subsequently found to have mitochondrial polymerase g gene *(POLG1)* mutations typical of Alpers-Huttenlocher disease, in a study at Newcastle University, UK. Brain MRI showed abnormal white matter signal in occipital and medial temporal lobes bilaterally. After discontinuing sodium valproate and substituting levetiracetam, liver function returned to normal over a 6-month period. Sequencing of *POLG1* is recommended in children with valproate-induced hepatic failure, and prior to commencing sodium valproate in young children (<3 years old) with aggressive focal epilepsy. Serum lactate, ammonia and liver function should be closely monitored in young children treated with valproate. (McFarland R, Hudson G, Taylor RW et al. Reversible valproate hepatotoxicity due to mutations in mitochondrial DNA polymerase g *(POLG1)*. **Arch Dis Child** Feb 2008;93:151-153). (Respond: Dr Robert McFarland, Mitochondrial Research Group, School of Neurology and Psychiatry, 4th Floor, Medical School, Framlington Place, Newcastle University, Newcastle NE2 4HH, UK).

COMMENT. The syndrome of diffuse progressive degeneration of the cerebral gray matter was first described by Alpers in 1931. Ford (1951) differentiated infantile and juvenile types and reported familial cases. Huttenlocher et al (1976) described coincident hepatic cirrhosis. Egger et al (1987) reported 13 cases treated at the Hospital for Sick Children, Great Ormond Street, London, 4 having received sodium valproate. A genetically determined, autosomal recessive, metabolic cause was suggested. Bicknese et al (1992) from Washington University, St Louis, MO, reported 6 patients with Alpers-Huttenlocher syndrome, 4 taking valproic acid (VPA), 2 of whom had a sibling with the same syndrome but no exposure to VPA. Siblings receiving VPA survived only 3 and 5 months after onset of seizures, whereas those not receiving VPA lived for 7 to 16 months. These authors proposed that many of the cases of VPA-associated hepatotoxicity represent undiagnosed hepatocerebral degeneration, Huttenlocher variant of Alpers' syndrome. In 2004, Naviaux et al described POLG mutations associated with Alpers' syndrome and mitochondrial DNA depletion. Patients with the syndrome treated with VPA have developed an irreversible liver failure and neurologic decline. The present case is exceptional, having a more favorable outcome.

A 17-year-old adolescent girl with Juvenile Alpers Disease is reported from the University of Otago, Wellington, NZ and other centers. (Wiltshire E et al. **Arch Neurol** Jan 2008;65:121-124). She presented with clusters of occipital seizures and clumsiness, and showed progressive memory impairment, slurred speech, and hemiparesis. She died of respiratory failure, cerebral degeneration, and liver necrosis. Mutational analysis of *POLG1* showed 2 novel mutations, similar to the abnormality in infantile Alpers disease.

NEUROMUSCULAR DISEASES

POLG1 MUTATIONS AND CHARCOT-MARIE-TOOTH DISEASE

A 35-year-old man first diagnosed with autosomal recessive Charcot-Marie-Tooth disease type 2 at 22 years of age had an abnormal gait and pes cavus at age 10 years. Molecular analysis of the *POLG1* (polymerase-g-1) gene in muscle biopsy showed 3 heterozygous mutations, in a study at Queen's Hospital, Romford; Newcastle University; and other centers in the UK. At 22 years, he had bilateral distal weakness and wasting of the extremities, clawing of toes, tremor of hands, loss of joint position and vibration sense, and nerve conduction studies consistent with axonal sensorimotor neuropathy. At 35 years, he was unable to walk and had developed a prominent no-no head tremor, upbeat and pendular nystagmus, cerebellar dysarthria and dysphagia, postural and action tremor, dysmetria, distal limb weakness and wasting, absent reflexes, and diminished sensation to all 4 modalities. Other affected family members include a brother and a sister who developed symptoms at 9 years. Muscle histochemistry findings showed denervation and reinnervation, and a mosaic defect of cytochrome c oxidase. Polymerase chain reaction of skeletal muscle DNA revealed multiple deletions of mtDNA. Segregation analysis in the family showed that heterozygous substitutions in the proband *POLG1* gene sequencing were inherited from the mother and father. The affected brother had the same genotype as that of the proband. (Harrower T, Stewart JD, Hudson G et al. *POLG1* mutations manifesting as autosomal recessive axonal Charcot-Marie-Tooth disease. **Arch Neurol** Jan 2008;65:133-136). (Respond: Patrick F Chinnery PhD, FRCP, Mitochondrial Research Group, The Medical School, Newcastle University, Room M41014, Framlington Place, Newcastle upon Tyne NE2 4HH, England; E-mail: p.f.chinnery@ncl.ac.uk).

COMMENT. *POLG1* mutations cause deletions and depletions of mtDNA , leading to a respiratory chain defect with organ dysfunction and the clinical phenotype of CMT. This case report and family are unusual since all 3 siblings had signs of peripheral neuropathy only, without signs of multisystem mitochondrial disorder. Tremor and ataxia developed late, without the ophthalmoplegia that is characteristic of the mitochondrial phenotype of sensory ataxic neuropathy with dysphagia and ophthalmoplegia (SANDO). The authors recommend that *POLG1* should be sequenced in patients with unexplained CMT, even in the absence of signs of mitochondrial disease.

Two novel connexin32 mutations cause early onset X-linked CMT in 2 Norwegian families. (Braathen GJ, et al. **BMC Neurology** 2007;7:19-28).

NEUROPATHY AND OTHER NEUROLOGICAL DISORDERS IN GAUCHER DISEASE TYPE 1

Neurological manifestations of 31 patients with Gaucher disease type 1 (GD1) were evaluated in a study at Miguel Servet University Hospital, Zaragoza, Spain. Twelve were males and 19 females, mean age 39 years (range 5-77). Age at diagnosis of GD was in early childhood or adolescence in 13

(42%) patients. Nerve conduction studies performed in 15 GD1 patients showed abnormalities in 12 (2 children); 26 – 40% showed reduced amplitude or abnormal wave forms in one to 3 nerves. Motor nerve conduction was normal, but sensory nerve conduction amplitude was reduced in 26% patients. Twenty-two patients receiving enzyme replacement therapy for 5-12 years showed neurological manifestations in 9. In adults, these were sensory neuropathy, parkinsonism, dementia, cognitive impairment and stroke; and in children, hypoacusia, myoclonus, and psychomotor delay. (Capablo JL, de Cabezon AS, Fraile J et al. Neurological evaluation of patients with Gaucher disease diagnosed as type 1. **J Neurol Neurosurg Psychiatry** February 2008;79:219-222). (Respond: Dr P Giraldo, Servicio de Hematolgia, Hospital Universitario Miguel Servet, Paseo Isabel La Catolica 1-3, 50006 Zaragoza, Spain).

COMMENT. Gaucher's disease, characterized by cerebroside storage in the reticuloendothelial system, occurs in 3 forms: Type 1) chronic GD, slowly progressive with visceral but rarely nervous system involvement; type 2) infantile GD with rapidly progressive CNS disease; and type 3) juvenile GD, with slowly progressive hepatosplenomegaly, intellectual deterioration, cerebellar ataxia, myoclonic seizures, and spasticity. An adult chronic GD is more common and may present in infancy, with rare CNS involvement. The above study shows that neurological abnormalities, including subclinical neuropathy, occasionally present in childhood GD1, and the classification of GD should be considered as a phenotype continuum.

DEMYELINATING DISEASES

SEROPREVALENCE OF NEUROMYELITIS OPTICA-IgG OF CHILDHOOD COMPARED TO ADULTS

The clinical and radiological characteristics and serostatus of neuromyelitis optica (NMO)-IgG in 87 children with inflammatory demyelinating CNS disorders were analyzed in a study at the Mayo Clinic, Rochester, MN, and other centers in the US, Canada, and Argentina. Seventeen patients had NMO and of these, 8 (47%) were seropositive. The prevalence of seropositivity was higher with relapsing NMO (7 of 9, 78%) than monophasic NMO (1 of 8, 12.5%, p=0.01). The majority of children with NMO (14 of 17) were enrolled from the program in Argentina, and few came from Canada. None showed oligoclonal bands in the CSF. MRI abnormalities were revealed in 9 (53%). After a follow-up of 36 months (range 1.2-126 months), 6.3% children with NMO were wheelchair-bound and 23% had severe visual impairment. One of 5 children with relapsing optic neuritis and none of 8 with monophasic optic neuritis was seropositive. Among 41 with relapsing-remitting multiple sclerosis, 9 with transverse myelitis, and 3 with ADEM, none was seropositive. The frequency of NMO-IgG in children is similar to that in adults. Longitudinally extensive

spinal lesions on MRI are not as predictive of NMO in children as in adults. (Banwell B, Tenembaum S, Lennon VA et al. Neuromyelitis optica-IgG in childhood inflammatory demyelinating CNS disorders. **Neurology** January 29, 2008;70:344-352). (Reprints: Dr Sean Pittock, Department of Neurology, Mayo Clinic, Rochester, MN 55905).

COMMENT. Neuromyelitis optica is characterized by monophasic or recurrent episodes of optic neuritis and longitudinally extensive transverse myelitis, either monophasic or recurrent. The autoantibody NMO-IgG is present in 73% of adults with NMO and is 92% specific for NMO and related disorders, recurrent optic neuritis or transverse myelitis. In children with NMO in the above study, 47% were seropositive. The role of NMO-IgG autoantibody in NMO is unknown, but it may be important in recurrent disease. An overview of NMO in children is provided in an editorial (Levy M et al. **Neurology** Jan 2008;70:334-335).

The most useful diagnostic feature of NMO or NMO-spectrum disorders in adults is a longitudinally extensive spinal cord lesion. This contrasts with the well-circumscribed foci of increased T2-weighted signal in multiple sclerosis, typically seen in adults. In children with MS, the discrete spinal lesions are common, but 14% also show the longitudinally extensive spinal lesions, rare in adults with MS. A longitudinally extensive spinal lesion in a child with demyelinating disease does not exclude a diagnosis of MS and is less predictive of an NMO-spectrum disorder than in adult patients.

Relationship between NMO and autoimmune disease. The association of NMO-IgG and non-organ-specific autoantibodies in patients with systemic lupus erythematosis (SLE) and in those with NMO spectrum disorder was evaluated at the Mayo Clinic and University of Lille, France (Pittock SJ et al. **Arch Neurol** 65:78-83). Patients with NMO were seropositive for NMO-IgG, and those with SLE without NMO were seronegative for this autoantibody. NMO-IgG is specific for distinguishing NMO spectrum disorder from multisystem autoimmune disorders. NMO may coexist with SLE and other autoimmune disease and is not a complication of SLE.

CORTICAL DEMYELINATION IN MULTIPLE SCLEROSIS

Cortical demyelination in CNS inflammatory demyelinating diseases is reviewed in an editorial and in a study by Moll NM et al (**Neurology** 2008;70:336-343). Cortical demyelination occurs in 3 different patterns: 1) leukocortical lesions, affecting both gray and white matter; 2) small perivenous intracortical lesions; and 3) widespread subpial demyelination. Type 3 is most abundant in multiple sclerosis (MS) and is related to chronic inflammation of the meninges. Cortical lesions in progressive multifocal leukoencephalopathy (PML) are similar to those in MS but are absent in HIV-encephalitis and adrenoleukodystrophy. T-cell inflammation is sparse in MS and PML cortical lesions in contrast to white matter lesions. Widespread subpial demyelination may be pathognomonic for MS and related inflammatory demyelinating diseases. (Lassmann H, Lucchinetti CF. Cortical demyelination in CNS inflammatory demyelinating diseases. **Neurology** Jan 29, 2008;70:332-336). (Reprints: Prof Dr Hans Lassmann, Div Neuroimmunology, Centre for Brain Research, Medical University of Vienna, Spitalgasse 4, A-1090 Wien, Austria).

COMMENT. Subpial cortical lesions in MS are related to an inflammatory process in the meninges. Cortical demyelination occurs mostly in progressive MS, and is invisible by conventional MRI.

Abnormal T-cell reactivities in childhood inflammatory demyelinating disease. (Banwell B et al. **Ann Neurol** Jan 2008;63:98-111). Peripheral T-cell proliferative responses to self-, dietary, and control antigens were evaluated in children with CNS inflammatory demyelination, recent-onset type 1 diabetes mellitus, nonautoimmune neurologic disorders, and healthy children. Those with inflammatory demyelination, CNS injury, and diabetes showed heightened T-cell reactivities to self-antigens. Nonspecific T-cell dysregulation is an early feature of childhood onset MS and diabetes. The study highlights the possible relation between dietary antigens (eg cow-milk reactivities) and autoimmune diseases. High milk consumption and early weaning to foreign protein diets have been proposed as a possible MS risk factor (Malosse D et al. **Neuroepidemiology** 1992;11:304-312). In the present study, the incidence of MS and diabetes was not different in patients exposed to infant formula and those breast-fed exclusively, but the analysis was limited.

DEGENERATIVE DISEASE

NEONATAL DIAGNOSIS AND TREATMENT OF MENKES DISEASE

Infants diagnosed with Menkes disease early by plasma neurochemical methods and treated early, within 22 days after birth, with copper replacement therapy, had a 92% survival rate vs 13% in those treated late, Median follow-up in 12 newborns treated early was 4.6 years compared to 1.8 years in 15 diagnosed and treated late. Abnormally low copper dependent, dopamine-B-hydroxylase activity was identified by measuring plasma catecholamine levels in infants at risk. Response to treatment occurred only in patients with ATP7A mutations that permit some residual copper transport. (Kaler SG, Holmes CS, Goldstein DS et al. Neonatal diagnosis and treatment of Menkes disease. **N Engl J Med** Feb 7, 2008;358:605-614). (Reprints: Dr Kaler, National Institute of Child Health and Human Development, National Institutes of Health, Bldg 10, Rm 5-2571, 10 Center Dr, MSC 1832, Bethesda, MD 20892).

COMMENT. Menkes disease is an X-linked recessive infantile neurodegenerative disease caused by deficiency of a copper-transporting ATPase, ATP7A. Enzymes that require copper as a cofactor (dopamine-B-hydroxylase, cytochrome coxidase) are decreased. Symptoms are delayed for 6 to 8 weeks after birth. The disease is characterized by hypotonia, seizures, failure to thrive, and death by 3 years of age. Biochemical markers such as low serum copper and ceruloplasmin are unreliable in the neonatal period since they are low in normal neonates and overlap with the values found in Menkes disease. A molecular diagnosis, involving measurement of dopamine, norepinephrine and other catecholamines in plasma, is necessary to identify cases before symptoms develop and for copper replacement therapy to be successful.