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INFECTIOUS DISORDERS

NEUROLOGIC COMPLICATIONS OF PARVOVIRUS INFECTION

Researchers in the Division of Pediatric Infectious Diseases at Albert Einstein College of Medicine, Bronx, New York conducted a PubMed database search of English and French literature for neurologic complications of parvovirus (PV) B19 infection or erythema infectiosum (fifth disease), Jan 1966 through July 2008. The diagnosis of PVB19 infection was confirmed by DNA-PCR (in 81% CSF and 85% serum samples) or detection of specific antibodies in 33% of CSF samples. Eighty-one cases of PVB19 neurologic disease were reviewed, mostly children; 62 (77%) had CNS manifestations and 19 had peripheral nervous system (PNS) disorders. The mean age was 15 years, and median age 9 years (range, 1 day to 68 years). CNS cases had a median age of 8 years, and PNS cases, 29.5 years. Male to female ratio was 1:1. The majority was immunocompetent; 32% had altered immunity. Viral or nonspecific flu-like symptoms were reported in 40%, and were more frequent in immunocompetent patients (P=.002); rash occurred in 38%, arthralgia in 17%, and lymphadenopathy in 16%. CNS manifestations included encephalopathy, encephalitis, or meningoencephalitis in 39/62 cases, meningitis (12), stroke (8), seizures, chorea, cerebellar ataxia, and opsoclonus. PNS manifestations included Guillain-Barre syndrome (1), neuropathies, brachial plexus neuropathy (8), and carpal tunnel syndrome (6 cases, all in adult women).

Encephalopathy or meningitis was reported mainly in children (mean age 15 years); seizures occurred in 46%, status epilepticus in 10% of patients. Prognosis was poor in 16/39 (41%); 4 died, 12 (31%) had sequelae (epilepsy, spastic quadriplegia), and 3 showed some improvement. Rare reports of intrauterine PVB19 infection with stroke and encephalopathy were not included in the review.

Laboratory findings in patients with CNS disease included elevated CSF WBC count

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in 31%, CSF protein elevation in 51%, and CSF glucose was decreased in 12%. MRI revealed white matter abnormalities in frontal or parietal lobes, or periventricularly, enlarged ventricles, and lesions in gray matter, brainstem, basal ganglia, and corpus callosum. EEG abnormalities included diffuse or focal slowing, and spike wave discharges. Brain biopsy of 2 patients with encephalitis showed chronic leptomeningeal inflammation and PVB19 DNA. Duration of CNS manifestations was 38 days (range, 2-198 days). Treatment with IV immunoglobulin (IG), with or without steroids, in 13 patients resulted in improvement in 8 (61%), and none of the patients who received IG or steroids died. Neurologic sequelae occurred in 22% of 77 patients with known outcome in the total group, some improvement occurred in 16%, and 56% recovered completely. Prevalence of sequelae was not different in immunocompetent patients compared to those with altered immunity, or in those with CNS manifestations, treated or untreated with IG with or without steroids. (Douvoyiannis M, Litman N, Goldman DL. Neurologic manifestations associated with parvovirus B19 infection. **Clin Infect Dis** June 2009;48:000). (Response and reprints: Dr Douvoyiannis. E-mail: mdouvoyi@montefiore.org).

COMMENT. The clinical manifestations of parvovirus B19 infection, listed in the AAP Red Book 27th ed, 2006, include erythema infectiosum (fifth disease), polyarthropathy, chronic anemia, aplastic crisis (with sickle cell anemia), and hydrops fetalis. The current article provides an extensive review of the neurological complications of PVB19 infection.

Parvovirus B19 infection is most commonly recognized by a distinctive rash, preceded for 7 to 10 days by a mild nonspecific illness consisting of fever, myalgia, and headache. The rash is intensely red, affecting the cheeks, trunk and extremities. The incubation period is 4 to 14 days.

WEST NILE VIRUS NEUROINVASIVE DISEASE

Epidemiological features of West Nile Virus (WNV) disease among children (<18 years of age) reported to the Centers for Disease Control and Prevention from 1999 through 2007 were analyzed and compared with those of adult WNV neuroinvasive disease (WNND), in a study at CDC&P, Fort Collins, CO. Of 1478 pediatric WNV cases reported, 443 (30%) had WNND, 1009 (68%) were classified as WN fever, and 26 (2%) were unclassified. The majority had onset between July and September. Among all cases of WNND reported, only 4% were in children. Of the 443 cases of pediatric WNND, 208 (47%) presented as meningitis, 163 (37%) as encephalitis or meningoencephalitis, 5 (1%) as acute flaccid paralysis (AFP), and 67 (15%) as unspecified WNND. The median age of WNND cases was 12 years. Three patients died. Median annual incidence of WNND was 0.07/100,000 children, in 40 states, primarily in South Dakota, Wyoming, and New Mexico. Of a total 11,081 WNND cases in the US, 4% occurred in children. The proportion classified as WNND was 30% and the same in children (<18 yrs) as in young adults (18-49 yrs). Older adults (>50 yrs) with WNND were more often classified with encephalitis (59%) than meningitis (23%), whereas in children and young adults, meningitis was preponderant (47% and 51%, respectively). (Lindsey NP, Hayes EB, Staples JE, Fischer M. West Nile virus disease in children, United States, 1999-2007. **Pediatrics** June 2009;123:e1084-e1089). (Respond: Nicole P Lindsey MS, Division of Vector-Borne Infectious Diseases, Centers for

Disease Control and Prevention, 3150 Rampart Road, Fort Collins, CO 80522. E-mail: frd3@cdc.gov).

COMMENT. According to the AAP Red Book (2006), the majority of pediatric WNV infections are asymptomatic, 20% have WNF, and <1% develop neuroinvasive disease. Risk of WNND increases with age and is highest in adults >60 years. Patients with WNND present with neck stiffness and headache, typical of aseptic meningitis, mental status changes of encephalitis, movement disorders such as tremor, seizures, or acute flaccid paralysis clinically similar to poliomyelitis or Guillain-Barre syndrome.

SEIZURE DISORDERS

TWINKLE MUTATIONS AND REFRACTORY STATUS EPILEPTICUS

Severe epileptic encephalopathy and refractory status epilepticus are reported in a 20-year follow-up of 23 patients with recessive Twinkle mutations studied at Helsinki University Central Hospital, Finland. Dominant mutations of the C10orf2 gene are linked with progressive external ophthalmoplegia, while recessive mutations cause mitochondrial DNA depletion and encephalopathy or hepatoencephalopathy, similar to phenotypes associated with recessive POLG1 mutations (eg Alpers syndrome). The authors had previously described infantile onset spinocerebellar ataxia caused by Twinkle mutations. On long-term follow-up, further clinical phenotypes developed, including refractory status epilepticus, migraine-like headaches, and psychoses. Myoclonic or focal clonic seizures occurred in 18 patients, progressed to epilepsia partialis continua in 15 and generalized status epilepticus in 13, 8 of whom died. The first episode of status epilepticus occurred between 15 and 34 years of age in homozygotes, and at 2 and 4 years of age in the compound heterozygotes. Status lasted from several days to weeks. Valproate caused elevation of liver enzymes in 2 patients and was discontinued. Phenytoin or fosphenytoin was ineffective and caused an elevation of liver enzymes. Oxcarbazepine, lamotrigine or levetiracetam was of benefit in some. MRI showed focal, stroke-like lesions, some hemispheric, resulting in edema, necrosis, and brain atrophy, including the hippocampus, and confirmed on neuropathology exam. (Lonnqvist T, Paetau A, Valanne L, Pihko H. Recessive twinkle mutations cause severe epileptic encephalopathy. **Brain** June 2009;132:1553-1562). (Respond: Dr Tuula Lonnqvist, Division of Child Neurology, Helsinki University Central Hospital, PO Box 280, Helsinki, 00029 Finland. E-mail: tuula.lonnqvist@hus.fi).

COMMENT. The authors comment that the infantile onset spinocerebellar ataxia (IOSCA) syndrome shares features with other mitochondrial recessive ataxia syndromes, including Friedreich's ataxia, mitochondrial spinocerebellar ataxia-epilepsy (MSCAE) syndrome and mitochondrial DNA polymerase gamma (POLG)-Alpers syndrome. IOSCA, a progressive neurodegenerative disease, is caused by homozygous or compound heterozygous C10orf2 gene mutations that code for the mitochondrial DNA helicase Twinkle. Status epilepticus, migraine-like headaches and psychiatric symptoms are also pathognomonic for the disease. These symptoms should alert the clinician to consider a mitochondrial encephalopathy in differential diagnosis.

BENIGN MYOCLONUS OF EARLY INFANCY

To redefine benign myoclonus of early infancy (BMEI), clinical and neurophysiologic features in 102 infants (60 male) with brief paroxysmal abnormal movements and normal neurologic and psychomotor development were studied at one center in Argentina and two in Italy. Infants with movements occurring only during sleep and those with abnormal EEG were excluded. Age at onset was 1-12 months (median 6.2 months). The nonepileptic paroxysmal motor phenomena included myoclonus in 23, brief tonic contractions and spasms in 38, shuddering in 35, atonia or 'negative' myoclonus in 4, and more than one motor phenomenon in 9. The movements generally involve the head and neck and upper limbs, and lower limbs are spared. EMG recordings of motor phenomena were characteristic of spasms, and associated with normal EEG. Episodes occurred only while awake in 87 (85%), both awake and asleep in 15 (15%), and were repeated several times a day, often (44% cases) in clusters. Except for 2 sisters with BMEI, no familial cases were found. Brain imaging and metabolic studies were normal. Episodes resolved at 6-30 months of age, the majority in the 2nd year. Two cases presented clinical and EEG features of benign focal epilepsy. Language and cognitive development were normal in all cases; fifteen (16%) developed hyperkinetic behavior without learning disorders. (Caraballo RH, Capovilla G, Vigevano F, Beccaria F, Specchio N, Fejerman N. The spectrum of benign myoclonus of early infancy: Clinical and neurophysiologic features in 102 patients. **Epilepsia** June 2009;50:1176-1183). (Respond: Dr Roberto H Caraballo, Neurology Department, Hospital de Pediatria, CP 1245, Buenos Aires, Argentina. E-mail: rhcaraballo@arnet.com.ar).

COMMENT. The authors conclude that the spectrum of the syndrome of BMEI is wide, each paroxysmal motor phenomenon has a characteristic EMG pattern with normal EEG, and the prognosis is benign. The syndrome is similar to that described by Lombroso CT and Fejerman N. (**Ann Neurol** 1977;1:138-143), and should be distinguished from West syndrome. A report of shuddering attacks in a 3-year-old girl found that flexion spasms without loss consciousness were controlled by propranolol (Barron TF, Younkin DP. **Neurology** 1992;42:258-259). A family history of essential tremor is reported in patients with shuddering attacks and some patients have both shuddering and tremor (Vanasse M et al. **Neurology** 1976;26:1027-1030). These authors propose that shuddering is an early manifestation of essential tremor. Intolerance to monosodium glutamate is reported in children with shuddering attacks (Reif-Leahrer L et al. **N Engl J Med** 1975:293:1204).

POST-TRAUMATIC DANCING EPILEPSY

Researchers at Thomas Jefferson University Hospital, Philadelphia, PA, report a case of "dancing epilepsy" in a 39-year-old, right-handed man who developed refractory complex partial seizures following head trauma at 15 years of age. During video-EEG monitoring of an episode of dancing movements with unresponsiveness lasting a few minutes, the ictal EEG was poorly localized, whereas the interictal EEG showed a left anterior temporal sharp wave focus. The MRI showed left frontal and right anterior temporal encephalomalacia and gliosis. The authors comment that dancing movements are a new behavioral manifestation of epilepsy, not typical of temporal lobe epilepsy, and more suggestive of frontal lobe epilepsy. (Bagla R, Khoury JS, Skidmore C. Teaching video neuroimages: dancing epilepsy.

Neurology June 2009;72;e114). (Response and reprints: Dr John Koury, 900 Walnut St, Ste 200, Philadelphia, PA 19107. E-mail: jskhoury@gmail.com).

COMMENT. Dancing as a form of epilepsy is a complex automatism, such as running (epilepsia cursiva) or bicycling movements. Lennox WG, in his book on epilepsy (1960;page 260) refers to episodes of running, spinning round and around, in seizures following head injury.

CHANGING TRENDS IN ANTIEPILEPTIC DRUG USAGE IN GIRLS

Concerns about potential effects on offspring have prompted a gradual change in antiepileptic drug usage in girls of child-bearing age in the last decade, according to a study at the School of Pharmacy and Institute of Child Health, University of London, UK. More females aged 12-18 years are prescribed lamotrigine (LTG) than carbamazepine or sodium valproate, and the 10-fold increase in LTG in females is significantly greater than the 5-fold rise for males. (Ackers R, Besag FMC, Wade A, Murray ML, Wong ICK. **Arch Dis Child** 2009;94:443-447) (Respond: Ian Wong. E-mail: ian.wong@pharmacy.ac.uk).

MOVEMENT DISORDERS

CLINICAL AND GENETIC ANALYSIS OF MYOCLONUS-DYSTONIA

Eighty-six myoclonus-dystonia (M-D) index patients from the Dutch national referral center underwent clinical and genetic evaluation in a study at University of Amsterdam, and other centers in the Netherlands and Belgium. Age of onset was 1 – 18 years in 48 (56%) and during adulthood in the remainder. Based on clinical examination, 24 cases were classified as definite M-D, 23 were probable, and 39 possible cases. According to previously published criteria, definite M-D had early onset and a positive family history. In the definite group, 50% carried an SGCE mutation; in the probable group, 4%; and in the possible cases, none had the mutation. (Ritz K, Gerrits MCF, Foncke EMJ, et al. Myoclonus-dystonia: clinical and genetic evaluation of a large cohort. **J Neurol Neurosurg Psychiatry** June 2009;80:653-658). (Respond: Dr MAJ Tijssen, Department of Neurology, Academic Medical Centre, University of Amsterdam, PO Box 22660, 1100 DD Amsterdam, The Netherlands. E-mail: m.a.tijssen@amc.uva.nl).

COMMENT. Myoclonus-dystonia is a genetically heterogeneous movement disorder with autosomal dominant inheritance. The clinical manifestations are myoclonus and dystonia predominantly in the upper body, and in adults may respond to alcohol. A mild dystonia often presents as cervical dystonia or writer's cramp; the myoclonus is rhythmic or arrhythmic, bilateral, asymmetric, involving mainly the proximal arms and axial muscles. The major gene locus maps to the epsilon-sarcoglycan gene (SGCE, DYT11) on chromosome 7q21-22. Various SGCE mutations are reported in several families and sporadic cases. In 50% cases of M-D, no mutation is identified.

DEVELOPMENTAL DISORDERS

CHANGING INCIDENCE, OUTCOME AND MANAGEMENT OF MYELOMENINGOCELE

Pediatric neurosurgeons at Children's Memorial Hospital, Chicago, review their long-term experience and the evolution of the etiology, diagnosis and management of patients born with myelomeningocele (MM) in 1975-1979 and followed for 25 years in a multi-disciplinary spina bifida clinic. Genetic factors and folic acid deficiency are implicated in the etiology of neural tube defects. Supplementation with folic acid has significantly reduced but not eliminated the risk of MM. The prevalence of spina bifida worldwide ranges from 0.17 to 6.39/1000 live births. Incidence varies with gender (girls > boys), ethnicity (increased in Hispanic and Northern Chinese), age (< 20 and >30 years more susceptible), geographic areas (in N America, higher in east and south cf west), and nutritional factors. Incidence was declining before use of folic acid, but following periconceptual multi-vitamin supplementation, a significant decrease occurred (MRC, 1991). Since 1992, US center for disease control recommends 400 mcg folic acid daily for women of reproductive age, and by 1998, fortification of all grain products. Incidence in US decreased 22.9%, when comparing period 1995-6 to 1998-9. Elective termination of pregnancy following prenatal diagnosis by serum alpha-fetoprotein screening and ultrasonography is also responsible for a declining incidence. The "lemon" sign and "banana" sign of Chiari II malformation are present on ultrasound after the 12th postmenstrual week. Fetal surgery for MM may arrest leakage of spinal fluid and prevent or reverse Chiari II malformation and hydrocephalus. Selective treatment for MM, as advocated by some authorities in the 1970, was generally not followed in the US, and today most centers treat all viable newborns aggressively without selection. The outcome of in utero closure awaits evaluation by the management of MM (MOM) study group.

Long-term outcome of non-selective treatment of 118 infants with MM born 1975-79, and followed at Children's Memorial Hospital, compared to a cohort born in 2000-2005, found a decline in the number of live births with MM: 16-32/year in the older cohort vs 1-13/year in the younger cohort of 40 children. The overall mortality in the older cohort at 20-25 year follow-up was 24%, the majority of deaths (18/28) occurring in infancy and pre-school years, secondary to hindbrain dysfunction or shunt malfunction. In the younger cohort, none have died during infancy and early childhood. Shunt placement has decreased from 86% in the older 1975-79 group to 65% in children born 2000-2005. (In a 2008 report from Great Ormond Street Hospital, London, UK, the rate of shunt placement is now 51%). The increased survival rate presents a challenge for pediatric and adult healthcare providers. (Bowman RM, Boshnjaku V, McLone DG. The changing incidence of myelomeningocele and its impact on pediatric neurosurgery: a review from the Children's Memorial Hospital. **Childs Nerv Syst** July 2006;25:801-806). (Respond: Dr Robin M Bowman, Division of Neurosurgery, Children's Memorial Hospital, 2300 Children's Plaza, PO Box 28, Chicago, IL 60614. E-mail: RBowman@childrensmemorial.org).

COMMENT. As with many congenital or early childhood chronic nervous system diseases, the transition period from pediatric to adult care poses problems. Pediatric subspecialists are frequently unfamiliar with adult care. Pediatric clinics are often

geographically separated from clinics for adults. Patients have difficulty separating from a team that has cared for them for two decades. The authors comment that shunt malfunction is a primary consideration in long-term care of MM, and adult colleagues need to become familiar with this problem. Learning and attention deficit disorders are additional troublesome complications of MM that require specialized treatment.

BRAIN TUMORS

CHANGING EPIDEMIOLOGY OF PEDIATRIC BRAIN TUMORS

Neurosurgeons at the Hospital for Sick Children, Toronto, Canada, analyzed and classified 1, 866 surgical pathology cases of brain tumors in children under age 19 years, treated 1980-2008. Astrocytomas accounted for 39.4%, (low-grade I/II 32.3%, grades III/IV 7.1%), medulloblastoma (10.6%), ependymoma (7.0%), craniopharyngioma (6.8%), meningioma (1.7%), and hypothalamic hamartoma (1.6%). Male preponderance (56.8%) occurred in all age groups, and particularly with medulloblastoma (M/F, 3/2). Classified by age group, ependymomas peaked at 0-2 years, and medulloblastoma at 3-5 years; astrocytomas increased in prevalence up to 9-11 years and then decreased. Distribution of tumors over the 3 decades showed little variation, except for medulloblastoma that showed a decreased percentage in 1990-99, and pilocytic astrocytoma (grade I) that increased steadily from 0.36% in 1980-89, to 7.32% in 2000-2008. The findings were consistent with published series from other countries, and changes in epidemiology may be attributed to changing classification systems, improved imaging and developments in epilepsy surgery. Under-reporting in the older groups (>15 years) may occur due to referrals to adult centers. (Kaderali Z, Lamberti-Pasculli M, Rutka JT. The changing epidemiology of paediatric brain tumours: a review from the Hospital for Sick Children. **Childs Nerv Syst** July 2009;25:787-793). (Respond: Dr JT Rutka, Division of Neurosurgery, The Hospital for Sick Children, The University of Toronto, Suite 1503, 555 University Ave, Toronto, Ontario, Canada M5G 1X8. E-mail: james.rutka@sickkids.ca).

COMMENT. The National Cancer Institute registry lists 488 CNS tumors reported in children in the state of Connecticut over a 39-year period; 467 were intracranial and 21 were spinal. Astrocytomas accounted for 28%, medulloblastomas 25%, ependymomas 9%, craniopharyngiomas 9%, and glioblastoma multiforme 9%. (Farwell JR et al. **Cancer** 1977;40:3123-3132). The incidence of medulloblastoma in the Connecticut series is double that found in the Toronto patients, whereas the percentages of other CNS tumors are similar. Of 6 series of childhood brain tumors (1949-1980) tabulated by Cohen ME and Duffner PK (**Brain Tumors in Children: Principles of Diagnosis and Treatment**. New York, Raven Press, 1984), one series reports medulloblastoma in 10.6% of 425 cases, similar to the Toronto series, whereas 5 series show percentages varying from 16.3% to 25% (mean, 20%). Over a 30-year period the incidence of specific types of childhood brain tumors had not changed appreciably. With an emerging microRNA brain tumor classification, the epidemiology of childhood brain tumors becomes more complicated. The influence of environmental risk factors (ionizing radiation, chemotherapeutic agents) is thought to be small (Baldwin RT et al. **Toxicol Appl Pharmacol** 2004;199:118-131).

PILOCYTIC ASTROCYTOMA WITH SPECIFIC GENE SIGNATURE

Researchers at Universite de la Mediterranee, and other centers in Marseille, France, using the microarray technique to compare the transcriptional profiles of five optic pathway, hypothalamo-chiasmatic and six cerebellar pilocytic astrocytomas, found that these 2 tumors are genetically distinct and topography-dependent entities. *NOTCH2*, a gene expressed in radial glia and involved in gliomagenesis, was upregulated in hypothalamo-chiasmatic pilocytic astrocytomas. A morphological study of the chiasma identified, in the floor of the third ventricle, a unique population of cells resembling radial glial cells from which the tumor originates. (Tchoghandjian A, Fernandez C, Colin C, et al. Pilocytic astrocytoma of the optic pathway: a tumour deriving from radial glia cells with a specific gene signature. **Brain** June 2009;132:1523-1535). (Respond: Prof D Figarella-Branger, Universite de la Mediterranee, 27 bd Jean Moulin 13285 Marseille cedex 05, France. E-mail: dominique.figarella-branger@univmed.fr).

COMMENT. Pilocytic astrocytomas are grade I gliomas of childhood that share features of astroglia and oligodendroglia, and affect the cerebellum or the optic pathway, especially the hypothalamo-chiasmatic region. The 2 tumors differ in their localization but also in prognosis. The cerebellar pilocytic astrocytoma has a benign course whereas the optic pathway tumor has a poor prognosis. The present study demonstrating distinct differences and the molecular basis responsible for the aggressive behavior of the optic pathway tumor may allow the development of new molecular targeted therapies.

CEREBELLAR ATAXIAS

ATAXIA-TELANGIECTASIA WITH HYPER-IgM SYNDROME

A group of eight children with ataxia-tengiectasia (A-T) who presented with serum Ig levels suggestive of hyper-IgM syndrome (HIGM) are reported from the Department of Paediatrics, Reinier de Graaf Gasthuis, Delft, and other centers in the Netherlands, Iceland, and Belgium. All patients ultimately showed clinical features of A-T (ataxia, telangiectasia, recurrent respiratory tract infection), and all had raised serum a-fetoprotein levels; in 7 the diagnosis of A-T was confirmed by DNA analysis. (Noordzij JG, Wulffraat NM, Haraldsson A, et al. Ataxia-telangiectasia patients presenting with hyper-IgM syndrome. **Arch Dis Child** June 2009;94:448-449). (Respond: Dr JG Noordzij, Department of Paediatrics, Reiner de Graaf Gasthuis, PO Box 5011, 2600 GA Delft, The Netherlands. E-mail: j.noordzij@rdgg.nl).

COMMENT. Hyper-IgM syndrome is a primary immunodeficiency disease that presents with recurrent infections, decreased serum immunoglobulin IgG and IgA and normal or raised IgM levels. Ataxia-telangiectasia also presents with recurrent infections, and at an early age the ataxia and telangiectasia may be absent. Immunodeficiency in A-T is associated with decreased serum IgG and/or IgA levels, and 10% of cases have normal or raised IgM levels. In the absence of typical clinical signs of A-T, the diagnosis may be confused with hyper-IgM syndrome. Elevated a-fetoprotein and low T lymphocytes distinguish A-T cases.