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J. GORDON MILLICHAP, M.D., F.R.C.P., EDITOR

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SLEEP DISORDERS

NARCOLEPSY AND ROHHAD SYNDROME

Investigators at Ghent University Hospital, Belgium; Radboud University Nijmegen Medical Centre, and Sleep Medicine Centre, Heeze, Netherlands, report a 7-year-old girl with rapid-onset obesity, hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD syndrome). In addition to dysfunction of endocrine, respiratory, and autonomic nervous systems, the patient developed daytime sleepiness, visual hallucinations, and episodic loss of facial muscle tone with slurred speech, suggestive of secondary narcolepsy and cataplexy. A nocturnal polysomnogram showing short sleep latency, sleep-onset REM period, and sleep fragmentation was compatible with narcolepsy, and absence of hypocretin-1 levels in the CSF was confirmatory. Noninvasive ventilation was attempted but was unsuccessful. Treatment was complicated by panic attacks and anxiety and by recurrent cardiac arrest in which she died. Ganglioneuroma or ganglioneuroblastoma was not detected. Autopsy was denied. (Dhondt K, Verloo P, Verhelst H, Van Coster R, Overeem S. Hypocretin-1 deficiency in a girl with ROHHAD syndrome. **Pediatrics** 2013 Sep;132(3):e788-92). (Response: Karlien Dhondt MD, Department of Pediatrics, Ghent University Hospital, Ghent 9000, Belgium. E-mail: karlien.dhondt@ugent.be).

COMMENT. Central hypoventilation syndrome is a rare heterogeneous disorder of early (congenital) or late, childhood onset of symptoms. Originally reported as Ondine's curse, or primary alveolar hypoventilation syndrome, and presenting at birth (Fishman LS, et al. **Am J Dis Child** 1965 Aug;110(2):155-61), the association of rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation is of late onset and has the acronym, ROHHAD (Rand CM et al. **Pediatr Res** 2011 Oct;70(4):375-8). The onset and timing of phenotypic features of

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the syndrome are variable, leading to delayed or missed diagnosis with potential fatality from hypoventilation and cardiorespiratory arrest.

Genetic testing of candidate genes in 15 children with ROHHAD syndrome. PHOX2B sequencing, the disease-causing gene in congenital central hypoventilation syndrome, revealed no mutations, demonstrating that late-onset ROHHAD is distinct from the congenital syndrome (Ize-Ludlow D, Gray JA, Sperling MA, et al. **Pediatrics** 2007 Jul;120(1):e179-88). In addition to hyperphagia and obesity, respiratory alveolar hypoventilation, thermal and other autonomic dysregulation, patients with ROHHAD have hyperprolactinemia, diabetes insipidus, and tumors of neural crest origin. The report of narcolepsy as a manifestation of this mainly respiratory syndrome may lend support to the theory of an autoimmune-mediated process as a possible cause of ROHHAD (Mahlios J, et al. The autoimmune basis of narcolepsy. **Curr Opin Neurobiol** 2013 Oct;23(5):767-73).

NARCOLEPSY/CATAPLEXY AND OCCULT NEUROBLASTOMA

Investigators at the University of Chicago and Northwestern University, Chicago, IL; University Hospital Southampton, UK; and Kiev Paediatric Hospital, Ukraine, report three children with narcolepsy and cataplexy subsequently diagnosed with neuroblastoma. Patient 1, a 3-year-old girl with gross motor delay and hypersomnia developed loss of tone and falling induced by laughter. Multiple sleep latency tests suggested narcolepsy. Six months later she became ataxic and neurologic examination revealed opsoclonus and divergent strabismus. MRI of the brain was normal, while CT scan of the chest demonstrated a 10 x 3 cm left paraspinal mass, T9 to T12. Surgical resection of a ganglioneuroblastoma, and treatment with adrenocorticotropin, plasmapheresis, iv immunoglobulin, and cyclophosphamide were of no benefit. After 2 years she developed central hypoventilation syndrome requiring continuous mechanical ventilation. Patient 2, a 2-year-old girl developed narcolepsy/cataplexy followed by muscle fatigue, ataxic gait and ptosis. A diagnosis of Lambert-Eaton myasthenic syndrome prompted a search for an occult neoplasm, and MRI of chest revealed a left costovertebral junction mass at T5-T9. Resection of a ganglioneuroblastoma followed by chemotherapy was followed by slow improvement and no recurrence of ptosis, weakness, hypersomnolence, or cataplexy. Patient 3, a 3-year-old girl presented with ataxic gait and frequent falls after varicella zoster. She developed narcolepsy/cataplexy with decreased CSF hypocretin level. MRI of pelvis revealed a paraspinal mass, confirmed as neuroblastoma at biopsy. Treatment with dexamethasone and chemotherapy resulted in rapid resolution of hypersomnia and cataplexy and gradual resolution of ataxia, followed by resection of the tumor. (Sinsioco C, Silver K, Forrest KM, et al. Narcolepsy with cataplexy as presenting symptom of occult neuroblastoma. **Pediatr Neurol** 2013 Jul;49(1):64-7). (Response: Dr Sinsioco, University of Illinois at Chicago, 1801 W Taylor St, Chicago, IL 60612. E-mail: sinsioco@uic.edu).

COMMENT. Narcolepsy with cataplexy is rare in early childhood and should prompt investigation to exclude neuroblastoma. Opsoclonus, ptosis, central hypoventilation, and dysautonomia may be present but are not invariable. (Koh PS, et al. **J Pediatr** 1994 Nov;125(5 Pt 1):712-6).

SEIZURE DISORDERS

FEBRILE SEIZURES AND FACE EMOTION RECOGNITION

Investigators at University-Hospital of Parma, Universities of Verona, Modena, and Bologna, Italy; and Epilepsy Clinic Las Condes, Santiago, Chile, studied facial emotion recognition ability in a group of 38 school-aged children with antecedent febrile seizures (FSs) and in an age- and sex-matched control group. Using Ekman and Friesen's Pictures of Facial Affect, the basic innate emotions studied were happiness, sadness, fear, anger, and disgust. Children with abnormal visuoperceptual abilities were excluded. Children with FSs showed lower recognition scores versus controls in both matching ($p<0001$) and labeling ($p=.001$) facial emotions. (Cantalupo G, Meletti S, Miduri A, et al. Facial emotion recognition in childhood: The effects of febrile seizures in the developing brain. **Epilepsy Behav** 2013 Oct;29(1):211-6). (Response: Dr Gaetano Cantalupo, Child Neuropsychiatry Unit, Department of Neuroscience, University-Hospital of Parma, Italy. E-mail: gcantalupo@gmail.com).

COMMENT. Emotion recognition abilities may be defective in school-aged children with a history of FSs, even in those with a single simple FS. FSs may alter long-term plasticity in extrahippocampal limbic regions, such as amygdala and insular cortex. Neural networks underlying facial emotion recognition involve the visual cortices, the amygdala, orbitofrontal cortex, insula, basal ganglia, and prefrontal cortex.

In patients with medial temporal lobe epilepsy (MTLE), common and widespread deficits of emotion recognition are well recognized (Meletti S, et al. **Neurology** 2003 Feb 11;60(3):426-31) but the above findings in children with simple FSs are new and suggest that the FS is not entirely benign.

RESCUE MEDICATION IN CHILDREN AT RISK OF PROLONGED CONVULSIVE SEIZURES

Investigators at the Institute of Child Health, Great Ormond Street Hospital, London, and other centers in the UK and Europe, explore the adequacy of treatment of children with prolonged convulsive seizures (defined as seizures lasting more than 5 min) occurring in school to prevent progression to status epilepticus and neurological morbidity. Already known is that medication should be given as quickly as possible, and administration of rescue medication in school depends on presence of a trained caregiver. Existing national recommendations include a parent's responsibility to request treatment for a child as needed, to provide all necessary medical information from the treating physician, and teacher volunteers responsible for administering medication should receive training from the school nurse or local health service. Areas for improvements include: 1) practical information to schools on treatment of prolonged convulsive seizures, 2) individual healthcare plan for the child, 3) a clear link between treating physician and school for each child who requires rescue medication, 4) responsible caregiver to receive specific training on rescue medication, 5) comprehensive guidance to ensure immediate treatment wherever seizure occurs, and 6) need for more information

on the experience of children, teachers, and emergency services regarding management of prolonged convulsive seizures occurring at school. (Cross JH, Wait S, Arzimanoglou A, et al. Are we failing to provide adequate rescue medication to children at risk of prolonged convulsive seizures in schools? **Arch Dis Child** 2013 Oct;98(10):777-80). (Response: Professor J Helen Cross. E-mail: h.cross@ucl.ac.uk).

COMMENT. In the past, a seizure lasting 30 min or longer was considered status epilepticus. Currently, experts classify any episode of seizure activity lasting 5 min or longer as status epilepticus. Once seizures persist for 5 to 10 min, they are unlikely to stop without treatment. Pre-hospital treatment with benzodiazepines will reduce seizure activity whereas delayed treatment is less successful, with risk of subsequent prolonged seizure activity, memory deficit, and learning difficulties. (Pellock JM. **J Child Neurol** 2007 May;22(5 Suppl):9S-13S).

A >15 min duration of a febrile seizure is one criterion for the definition of a complex seizure, but a recent FEBSTAT study supports a redefining of simple vs complex seizure, limiting the duration of a simple febrile seizure to no longer than 10 min (Hesdorffer DC, et al. **Ann Neurol** 2011 Jul;70(1):93-100).

Spontaneous seizures and febrile seizure duration. Data in support of a shorter 5-10 min cut off for a simple FS were obtained in a comparative study of 86 consecutive patients with FSs of short and long duration (Millichap JG, et al. **Neurology** 1960 Jul;10:643-53; Millichap JG. **Febrile Convulsions.** New York: Macmillan, 1968, pp 101-3). In 38 patients with FS <5 min duration, 7.9% developed spontaneous seizures; in 21 with FS 5-10 min duration, 9.5%; in 14 with FS 10-20 min duration, 14%; and in 13 with FS >20 min duration, 38% had spontaneous seizures. The difference in spontaneous seizure incidence in patients with FS of 5 and 10 min duration was not significant whereas that between the 10 and >20 min FS duration was very significant. The prompt treatment within 5-10 min of onset of a convulsive seizure (febrile or non-febrile) is recommended, using an age-appropriate benzodiazepine preparation (rectal diazepine. intranasal lorazepam, or buccal midazolam). (Sofou K, et al. **J Child Neurol** 2009 Aug;24(8):918-26). For the optimal outcome of children at risk of prolonged convulsive seizures, rescue treatment for administration at home or in the school should be available.

PROGNOSIS OF EARLY ONSET ABSENCE EPILEPSY

Investigators from University of Chieti and several other centers in Italy conducted a multicenter retrospective 36-month follow-up study of the electroclinical course of epilepsy in all children with typical absence seizures (TAS) starting in the first 3 years of life. Two groups of patients were compared: 1) 111 who fulfilled Panayiotopoulos's criteria for childhood absence epilepsy (CAE) classified as having pure early onset absence epilepsy (P-EOAE), and 2) 77 who did not satisfy the criteria and were classified as nonpure EOAE (NP-EOAE). The 2 groups were also stratified according to the number of antiepileptic drugs used to obtain initial seizure control.

Patients with pure EOAE showed earlier initial seizure control (p=0.030) and better seizure-freedom (p=0.004) than those with NP-EOAE. P-EOAE patients had no mutation in SLC2A1 gene and no abnormal neuroimaging. Among the NP-EOAE

patients, those receiving tritherapies showed increased risk of structural brain abnormalities (p=0.001) or SLC2A1 mutations (p=0.001) but fewer myoclonic features (p=0.031) and worse seizure-free survival (p=0.047) than those treated with mono-and biotherapy. Children with NP-EOAE had an increased risk of relapse during follow-up compared to P-EOAE patients. (Agostinelli S, Accorsi P, Beccaria F, et al. and on behalf of the Societa Italiana Neurologia Pediatrica Collaborative Working Group. **Epilepsia** 2013 Oct;54(10):1761-70). (Response: Dr Alberto Verrotti, Department of Pediatrics, University of Chieti, Italy. E-mail: averrott@unich.it).

COMMENT. Children <3 years old with early onset TAS who meet the modified Panayiotopoulos's criteria for childhood absence epilepsy (CAE) have a good prognosis, whereas those not meeting the criteria have an increased risk of relapse at long-term follow-up.

Panayiotopoulos's definition of CAE (Panayiotopoulos CP. **Epilepsia** 2008 Dec;49(12):2131-9) is abridged as follows: 1) age at onset between 4 and 10 years (modified to within the first 3 years for this study); 2) normal neurologic exam; 3) brief (4-20 sec) and frequent (many per day); 4) EEG 3-4 Hz spike and slow-wave complexes. Exclusion criteria include 1) other types of seizure; 2) eyelid myoclonia, perioral myoclonia, head and limb myoclonic jerks; 3) EEG polyspikes; 4) photic precipitation of clinical seizures.

TRANSITION FROM PEDIATRIC TO ADULT HEALTH CARE FOR DRAVET SYNDROME PATIENTS

Investigators from University Hospital of Rennes; Necker Hospital, Paris; and University Paris Descartes, France used a questionnaire to study the transition and transfer from pediatric to adult health-care system in patients with Dravet syndrome and their families. The diagnosis of Dravet syndrome was made during the first 2 years and was followed by a long follow-up in the pediatric health-care. A response rate of 85% was obtained from 60 families, and 61% experienced a transfer. Positive factors for a smooth transition included 1) the quality of transition preparation (p<.000001), 2) a longer duration of follow-up by the same child neurologist (p<.001), 3) the availability of the child neurology staff (p<.01), 4) transfer into adult health-care after the age of 18 (p<.01), and 5) a stable medical condition before transfer (p<.05). The age of transfer (18.7 +/- 4 years) was close to the legal age of adulthood, and the association of mental retardation with severe epilepsy had little impact on transfer age. All families reported a positive experience in the pediatric health care system. Child neurologists were considered as welcoming, available, and helpful. Almost all patients transferred reported no gap in the process. Their experience in the adult health-care system was similar to pediatric care. Only 9% patients contacted their child neurologist after the transfer, and 79% continued follow-up with the same neurologist. Preparation for transfer began an average of 1 year before transition, which is shorter than that generally recommended for chronic illnesses. (Kuchenbuch M, Chemaly N, Chiron C, Dulac O, Nabbout R. Transition and transfer from pediatric to adult health care in epilepsy: A families' survey on Dravet syndrome. **Epilepsy Behav** 2013 Oct;29(1):161-5). (Response: Dr Rima Nabbout, Hospital Necker Enfants Malades, Paris. E-mail: rimanabbout@yahoo.com).

COMMENT. A Canadian study considering strategies for transitioning to adult care for youth with Lennox-Gastaut syndrome and related disorders (Camfield PR, et al. **Epilepsia** 2011 Aug;52 Suppl 5:21-7) found that an adult practitioner took less time with the patient and family, and the adult provider was not familiar with the medical disorder. A survey of 133 symposium attendees indicates much dissatisfaction with the process of transition, especially for patients with intellectual handicap. Suggestions to improve transition include identifying a willing adult service, a multidisciplinary approach, adolescent clinics, and attention to vocational training and/or special education.

MOVEMENT DISORDERS

HYPEREKPLEXIA, APNEAS, DEVELOPMENTAL DELAY, AND GENETIC CORRELATIONS

Investigators at Swansea University and other centers in the UK, Australia, and Belgium studied the genotype-phenotype correlations in 97 individuals with a clinical diagnosis of hyperekplexia; 61 cases had mutations in GLRA1, 24 cases in SLC6A5 and 12 in GLRB. All gene-positive cases presented in the neonatal period and clonazepam was effective treatment in 95%. Hyperekplexia is a predominantly recessive inheritance, and is dominant in 16%. In 35 gene-negative cases, presentation was after the first month of life.

The characteristic symptoms of hyperekplexia are 'stiffness, startles and stumbles.' In addition, 50 of 89 patients had apnea attacks and 47 of 92 were developmentally delayed. Recurrent infantile apneas occurred more frequently in patients with SLC6A5 mutations than in those with GLRA1 mutations. Developmental delay occurred more frequently in patients with GLRB and SLC6A5 mutations than in those with GLRA1 mutations; 92% of GLRB cases had a mild to severe delay in speech acquisition. The developmental delay especially in speech may represent failure of developmental neural networks or migration defects. (Thomas RH, Chung S-K, Wood SE, et al. Genotype-phenotype correlations in hyperekplexia: apnoeas, learning difficulties and speech delay. **Brain** 2013 Oct;136(Pt 10):3085-95). (Response: Dr Rhys H Thomas, Institute of Life Science, College of Medicine, Swansea University, Singleton Park, Swansea, SA2 8PP. E-mail: Rhys.Thomas@swansea.ac.uk).

COMMENT. Hyperekplexia was first described by Kok O, and Bruyn GW (**Lancet** 1962;279(7243):1359) in 29 members of one family and occurred as a dominant autosomal transmission. Hypertonia is present at birth and becomes less pronounced during the first year of life but later leads to repeated falls. The name "hereditary stiff baby syndrome" was used by Lingam S, et al. (**Am J Dis Child** 1981 Oct;135(10):909-11). The child has a fixed stare and an expression of anxiety. Hypertonia diminishes during sleep and increases with the slightest psychic or tactile stimulus. Nose tapping elicits the hyperekplexic response and is included in the neonatal exam of infants at risk. Attacks of hypertonia that involve the respiratory muscles can lead to apneas that endanger life. The EMG shows persistent activity abolished by diazepam or clonazepam; the EEG is normal.

Early genetic testing is recommended for symptomatic hyperekplexic neonates and possibly preconception counseling for those at risk for GLRB and SLC6A5 mutations. Recessive inheritance of hyperekplexia is associated with an increased risk of learning difficulties and developmental delay, particularly in speech acquisition. Severe recurrent neonatal apneas occur in approximately 50% of cases, particularly those with mutations in GLRB and SLC6A5. Stiffness, startle and stumble are the cardinal features of hyperekplexia.

DEMYELINATING DISORDERS

SINGLE CENTER EXPERIENCE OF ACUTE DISSEMINATED ENCEPHALOMYELITIS

Investigators at Department of Pediatrics, Neurology Division, Adana Medical Research Center; and Division of Child Neurology, Ankara, Turkey, retrospectively evaluated 15 children with acute disseminated encephalomyelitis (ADEM) in children from the center in Adana. ADEM was seasonal, 73.3% cases presenting in winter or spring. The majority (13/15, 86.7%) had an acute febrile upper respiratory illness 2 to 40 days before presentation. Five children had serological evidence of specific triggers: mycoplasma (2), influenza-A (H1N1) (1 child), and Epstein-Barr virus (2 children). One patient had received a combined vaccine (DTPP-Haemophilus influenzae B) 6 weeks before onset. Gait disturbance (12/15, 80%) was the most common presenting symptom, followed by altered consciousness (10/15, 66.7%), fever (7/15, 46.7%), headache (4/15, 26.7%), seizures (4/15, 26.7%), meningismus (4/15, 26.7%), and vomiting (3/15, 20%). EEG recorded in 8 patients showed generalized slowing in 3 patients and focal epileptiform discharges in 1. CT scan obtained in 14 patients showed lesions in only 3 cases, whereas MRI revealed cerebral lesions in all 15 patients (with complete resolution following treatment in 12, partial in 2). Treatment in all cases was a standard protocol of 3 to 5 days of IV methylprednisolone and IV immunoglobulin for patients with persistent deterioration. Oseltamivir and clarithromycin were administered in patients with influenza-A and mycoplasma. Follow-up evaluation ranged from 0.6 to 4 years (median 1.8 years). Neurologic symptoms and signs resolved in 13 patients; one patient had severe neurologic sequelae, and one had recurrent attacks and a final diagnosis of MS. (Erol I, Ozkale Y, Alkan O, Alehan F. Acute disseminated encephalomyelitis in children and adolescents: a single center experience. **Pediatr Neurol** 2013 Oct;49(4):266-73). (Response: Dr Erol, Division of Pediatric Neurology, Adana Teaching and Medical Research Center, Baskent University Faculty of Medicine, Adana, Turkey. E-mail: ilknur_erol@yahoo.com).

COMMENT. ADEM is an inflammatory demyelinating disease of the CNS that follows an infection or vaccination in three-quarters of the cases.

Post-vaccination ADEM. Several vaccines have been implicated including rabies, DTP, smallpox, measles, mumps, rubella, pertussis, and influenza (Huynh W et al. Post-vaccination encephalomyelitis: literature review and illustrative case. **J Clin Neurosci** 2008 Dec;15(12):1315-22). A patient presenting with bilateral optic

neuropathies within 3 weeks of "inactivated" influenza vaccination had a delayed onset of ADEM 3 months post-vaccination.

A case of ADEM is reported in a 34-month-old boy who presented with a seizure and left-sided weakness 5 days after vaccination against novel influenza A (H1N1). Following IV corticosteroids, symptoms improved and he recovered without neurologic sequelae (Lee ST et al. An adverse event following 2009 H1N1 influenza vaccination: a case of acute disseminated encephalomyelitis. **Korean J Pediatr** 2011 Oct;54(10):422-4). A PubMed search found 5 reports of ADEM following 2009 H1N1 vaccination, one occurring simultaneously with Guillain-Barre disease (Hoshino T et al. **Intern Med** 2012;51(12):1595-8). With increased demand for mandatory vaccination for health-care workers, recognition of the occasional association of ADEM with influenza vaccine should prompt early diagnosis and steroid therapy.

DEVELOPMENTAL DISORDERS

DIAGNOSTIC ALGORITHM FOR MICROCEPHALY

Investigators from Addenbrooke's Hospital, Cambridge, UK, provide a diagnostic structure to follow when presented with a child with microcephaly. An occipital-frontal-circumference (OFC) of >3SD below the age and sex expected is the definition used for microcephaly. "Primary" microcephaly is present at birth and "secondary" microcephaly develops after birth. Serial OFC measurements that follow the growth curve suggest a primary microcephaly, whereas an OFC that falls relative to the growth curve is usually a secondary microcephaly. In *primary* cases check for maternal and environmental factors including the TORCH screen, MRI, and fetal brain imaging. Cases with dwarfism and those with dysmorphic features and/or congenital anomalies may be recognized by phenotype (e.g. Cornelia de Lange syndrome- synophrys, dwarfism, limb anomalies) or may require cytogenetic testing. *Secondary* microcephaly cases may be static or progressive. The majority of chromosome disorders are associated with developmental delay and secondary microcephaly (e.g. Miller-Dieker syndrome caused by deletion of chromosome 17p13.3). Larger deletions are associated with a more severe phenotype of lissencephaly/pachygyria, and smaller deletions involve the LIS gene and a less severe form of lissencephaly. Rubinstein-Taybi syndrome is a Mendelian disorder causing secondary microcephaly and learning disorders. The diagnosis is clinical (distinctive facies, broad thumbs/big toes and postnatal growth retardation) and is confirmed by mutations in the CREBBP, EP300 or SRCAP gene.

If secondary microcephaly is associated with progressive neurologic findings, metabolic diseases should be considered. Genetic disorders such as Rett, PEHO, Cockayne, and Cohen syndromes are examples of secondary microcephaly where diagnosis by DNA testing is available. (Woods CG, Parker A. Investigating microcephaly. **Arch Dis Child** 2013 Sep;98(9):707-13). (Resp.: Dr. C. Geoffrey Woods. Clinical Genetics, Addenbrooke's Hospital, Cambridge, UK. E: cw347@cam.ac.uk).

COMMENT. A knowledge of neurological syndromes is helpful in the differential diagnosis of microcephaly. (Millichap JG. **Neurological Syndromes : A Clinical Guide to Symptoms and Diagnosis.** New York: Springer, 2013:279).