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CLiPPs

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CLiPPs (**C**urrent **L**iterature in **P**ediatric **P**sychosomatics) *is a pertinent article review through the AACAP Physically Ill Child Committee for psychosomatic clinicians from a range of medical science journals and literature. We are very excited for our inaugural issue is finally here and have already begun working on our Summer 2016 edition.*

Seropositive vs Seronegative Autoimmune Panencephalitis (SNAPE)

Background and Objectives: There is a growing recognition of autoimmune encephalitis such as anti-NMDA receptor encephalitis as a cause of psychiatric symptoms and altered mental status in children. Some patients may present with signs and symptoms suggestive of an autoimmune process but do not test positive for known autoantibodies. The objective of this study was to describe the clinical features of children with suspected autoimmune encephalitis and compare findings and outcomes of patients with and without identified CNS autoantibodies. Some authors refer to this latter entity as SNAPE (seronegative autoimmune encephalitis).

Methods: Serum samples of 111 children presenting with encephalopathy plus neuropsychiatric symptoms, seizures, movement disorders and/or cognitive dysfunction seen at 5 tertiary referral centers in the UK with encephalopathy were sent to the Oxford lab for CNS autoantibody testing. A blinded clinical review panel identified 48 probable cases of autoimmune encephalitis. Clinical data including demographic information, features of presentation, imaging and other laboratory testing results, response to immunotherapy and other outcomes were compiled, with reviewers blinded to autoantibody testing results.

Results: Serum antibodies were detected in 44% of the patients with probable autoimmune encephalitis. Patients ranged between just under 2 to 18 years of age. Antibody negative patients were clinically similar to those with identified auto-antibodies and had similar response to immunotherapy. Seizures (86%) and behavioral changes (63%) were the most common associated clinical findings. EEGs were abnormal in 70% of patients. 52% of patients receiving immunotherapy experienced a complete recovery, as opposed to 28% of untreated patients.

Conclusions/Commentary: Patients with probable autoimmune encephalitis share clinical features regardless of presence of detected autoantibodies. Treatment response to immunotherapy was

generally positive, with 94% of treated patients classified having some response and 58% experiencing a full recovery. These data suggest that an autoimmune work-up should be strongly considered for patients who present with encephalopathy and at least one of the following features: neuropsychiatric symptoms, seizures, movement disorders, or cognitive dysfunction.

Take-away: SNAPE happens. If autoimmune encephalitis is strongly suspected, clinicians should consider immunotherapy even in cases where tests for known autoantibodies are negative.

References:

1. Leypoldt F, Armangue T, Dalmau J. Autoimmune encephalopathies. *Ann NY Acad Sci* 2015;1338:94-114.
2. Najjar S, Pearlman DM, Devinsky O. Neuropsychiatric Autoimmune Encephalitis without VGKC-Complex, NMDAR, and GAD Autoantibodies: Case Reports and Literature Review. *Cogn Behav Neurol* 2013;26(1):36-49.
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5. Bale JF. Virus and Immune-Mediated Encephalitides: Epidemiology, Diagnoses, Treatment, and Prevention. *Pediatr Neurol* 2015;53:3-12.

Reviewer: Emily Katz, M.D., Brown University Warren Alpert Medical School/ Hasbro Children's Hospital, Providence, RI.

Source: Hacohen Y, Wright S, Waters P, et al. Paediatric autoimmune encephalopathies: clinical features, laboratory investigations and outcomes in patients with or without antibodies to known central nervous system antigens. J Neurol Neurosurg Psychiatry 2013;84:748-755. Pubmed link can be found here.

PTSD in Critical Illness Survivors

Background and Objective: Posttraumatic Stress Disorder (PTSD) symptoms in critical illness survivors has gained increasing recognition in the past 5 years with the number of studies published on this topic more than doubling, including studies regarding intervention and treatment. The purpose of this review and metaanalysis was to evaluate the prevalence of PTSD symptoms in adult general critical illness survivors and synthesize risk factors for PTSD symptoms, associations between PTSD and quality of life, and effectiveness of prevention and treatment interventions.
Methods: A systematic review of the literature on PTSD, psychometrics, critical care, and respiratory distress was performed via PubMed, Embase, CINAHL, PsycINFO, and Cochrane Library looking at all studies through March 2014. Studies were included if the study population consisted of adult critical illness survivors and PTSD assessment was conducted using a validated measure greater than 1 month

post-ICU in the home environment. Studies focusing on pediatric patients or a specialty ICU were excluded, as were case series with less than 10 patients. For studies that used the Impact of Event Scale (IES) to measure PTSD symptoms, pooled prevalence IES score was calculated.

Results: The search identified 2,817 titles/abstracts, with 40 eligible articles on 36 unique cohorts (n = 4,260 patients). In all studies, the point prevalence of PTSD symptoms ranged from 4% to 62%. Two studies assessed PTSD symptoms with a semi structured psychiatric interview; the remaining used questionnaires, most commonly the IES. Metaanalysis of the studies that used the IES scale showed a pooled prevalence of clinically important PTSD symptoms (using IEDS thresholds greater than or equal to 35) of 25% at 1-6 months post-ICU and 17% 7-12 months post-ICU.

All six studies that evaluated mental health-quality of life, associated worsened quality of life with greater PTSD symptoms. Pre-ICU psychopathology, benzodiazepine use, and early post-ICU memories of frightening ICU experiences (hallucination, paranoid delusions, and nightmares) were associated with PTSD symptoms in studies. Age, gender, daily interruption of sedation, light versus deep sedation protocols, duration or presence of delirium, severity of illness, ICU length of stay, admission diagnosis, and mechanical ventilation were not associated with PTSD in the majority of the studies. Two European studies associated an ICU diary with a significant reduction in PTSD symptoms at 3-12 month follow-up.

Conclusions/Commentary: This review and metanalyaiss found that clinically important PTSD symptoms occur in one of five patients with critical illness in the first 12 months post- ICU, a prevalence comparable to war-time combat. Greater PTSD symptoms are associated with worse quality of life. Preexisting psychopathology, benzodiazepine usage, and early memories of frightening ICU experiences were associated with PTSD symptoms. Interestingly, the two studies that evaluated the association between delirium and later PTSD symptoms did not find an association, perhaps due to the powering difficulties and the high number of individuals with delirium.Treatment studies are still limited, but encouraging for the use of ICU diaries, a low-cost intervention that has become standard of care in some European ICUs (www.icu-diary.org). Additional research is needed to further assess treatment and prevention interventions and to discover the generalizability of these findings to the pediatric population.

Take-away: PTSD symptoms are common in adult critical care illness survivors over a 1–year follow-up period, with higher prevalence in those who had comorbid psychopathology, received benzodiazepines, and had early post-ICU memories of frightening ICU experiences. Additional work is needed to continue identifying risk factors for PTSD in critical illness and develop effective prevention and treatment interventions in pediatric patients.

References:

1. Jones C, Backman C, Capuzzo M, et al. Intensive care diaries reduce new onset post traumatic stress disorder following critical illness: A randomized, controlled trial. *Crit Care.* 2010; 14:R168.

2. Wade D, Hardy R, Howell D, et al. Identifying clinical and acute psychological risk factors for PTSD after critical care: a systematic review. *Minerva Anestesiol.* 2013; 79:944-963.

Reviewer: Lisa Giles, M.D., University of Utah School of Medicine / Primary Children's Hospital, Salt Lake City, UT.

Source: Posttraumatic Stress Disorder in Critical Illness Survivors: A Metaananysis. *Critical Care Medicine.* May 2015; 43 (5): 1121-1129. Pubmed link can be found here.

Risk of seizure in patients with ADHD on methylphenidate

Background and Objective: Methylphenidate's (MPH) safety for ADHD treatment in children without epilepsy is well-established. However, there is less research examining safety of MPH in children with comorbid ADHD and epilepsy or comorbid ADHD and interictal epileptiform discharges (IED) without the clinical seizures. This study examined whether the MPH use was associated with the development of seizures in children with ADHD and IED only during 2 years follow-up.

Methods: EEGs were obtained on 517 children aged 5- to 14-years-old with ADHD. Those with ADHD and IED at baseline (n = 39) were compared to matched ADHD children without IED (n = 39) and followed up longitudinally for 2 years. IED were defined as spikes or spikewave complexes, isolated or occurring serially (in runs) without evident clinical signs of a seizure. They were assessed at 1- and 2-year follow-up for seizure occurrence and frequency and use of MPH. MPH was administered in dosage 0.5–1.2 mg per kilogram either three times daily (short-acting MPH) or once per day (slow-acting MPH).

Results: At baseline, 12 out of 39 children with IED (30.8%) were diagnosed with epilepsy and treated with antiepileptic medications. At baseline, 36 out of 39 of these children with IED were taking MPH and 37 controls without IED were treated with MPH ($p = 0.64$). At both 1- and 2-year follow-up, there were no differences in MPH use between the IED and non-IED groups ($p = 0.19$). Only 3 patients, all with pre-existent seizures at baseline, had experienced a seizure during the follow-up; however there was no change in seizure frequency in these patients from baseline to follow-up.

Conclusions/Commentary: The results of this long term study provide support for the safety of MPH to treat ADHD in children with epileptogenic EEGs and in those with epilepsy. In children with IED, only those with a history of pre-existing epilepsy experienced seizures over the course of the 2 years. Importantly, in these children, the frequency of seizures did not increase. The use of MPH was similar in the both groups (with and without IED).

Take-away: The use of MPH for children with ADHD did not predict increased risk of development of seizures in children with epilepsy and IED only.

References:

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2. Gonzalez-Heydrich et al. Comparing stimulant effects in youth with ADHD symptoms and epilepsy. *Epilepsy Behav 2014; 36:102-107.*

Reviewer: Sigita Plioplys, Ann & Robert H. Lurie Children's Hospital of Chicago and Northwestern University Feinberg School of Medicine, Chicago, IL

Source: Socanski D, Aurlien D, Herigstad A, Thomsen PH, Larsen Tk. Attention deficit/hyperacticity disorder and interictal epileptiform discharges: It is safe to use methylphenidate? *Seizure* 2015; 25: 80-83. Pubmed link can be found here.

Atypical Anti-Psychotics in Infant and Toddler Delirium

Background and Objective: Recognition of delirium in pediatric settings, and the morbidity associated with it, is increasing. While the clinical presentation of delirium in school age and adolescent patients resembles that in adults, infants and toddlers present unique diagnostic challenges requiring developmentally-informed clinicians and standardized assessment tools. Atypical antipsychotics are increasingly administered to pediatric patients, including infants and toddlers, for the treatment of delirium despite the absence of randomized, blinded clinical trials addressing their safety or efficacy. This retrospective study specifically addresses the efficacy and tolerability of Risperidone and Olanzapine in infants and preschoolers.

Methods: A retrospective chart review of all inpatient psychiatric consultations at Children's Hospital of Los Angeles between January 1, 2004 and December 31, 2007 was performed to identify patients with delirium less than 3 years old and atypical anti-psychotic usage. The Delirium Rating Scale (DRS) was applied and scored retrospectively along with DSM-IV TR criteria for delirium prior to initiation, and after discontinuation, of the atypicals. While standard non-medical interventions for delirium were provided to all subjects, these were not the focus of the study.

Results: The review identified 19 patients with delirium with an age range of 7-34 months and mean age 20.5 months, 10 boys and 9 girls. All patients received either risperidone or olanzapine; patients receiving other atypicals, if any, were excluded. Starting doses of risperidone (3 patients) were 0.05-0.1 mg qhs or bid, and for olanazpine (16 patients) 0.625-1.25 mg qhs or bid. Range of days of dosing for atypicals was between 2 and 151 days. Dose titrations were made to control agitation and insomnia. The most prominent symptoms in study subjects were sleep disturbance, irritability, agitation, and impaired attention. As these symptom clusters (except sleep) are not identical to scored domains of

the DRS, pre- and post-treatment scores were reported for domains that appear to be closest: Mean "psychomotor behavior" , "sleep-wake disturbance" and "mood lability" scores all fell from 3 pre-treatment to 0 post-treatment. All 19 subjects were judged to have exhibited symptoms in all three domains prior to treatment. Total mean DRS score across subjects was 16.8 pre-treatment and 6.2 post-treatment ($p<0.0001$), using Minitab Statistical Software®. There were no reported instances of abnormal tone, movement, or cardiac arrhythmias in any subject. Three patients (16%) died of their underlying condition.

Conclusion/Commentary: This study provides important perspective on an increasingly recognized and challenging clinical problem faced by pediatricians and child psychiatrists in acute care settings such as pediatric intensive care units (PICU): A recent PICU study of 99 subjects found a delirium prevalence of 21%, 0-5 year olds accounting for 54% of the total[1]. Most prevalent symptoms in the current study were inattention, sleep disturbance, and agitation. The authors' principle finding was improvement in symptoms in all 19 subjects on initiation of either olanzapine or risperidone, DRS scores falling from 3 to 0 pre and post-treatment in the "psychomotor behavior", "sleep/wake disturbance" and "mood lability" categories. There are no published randomized controlled trials of antipsychotics in pediatric patients with delirium of any age, yet clinicians require tools to guide treatment for a disorder with well documented risks of morbidity and mortality. The current study accomplishes this goal by sharing the authors' favorable experience in efficacy and tolerability of two atypical antipsychotics in a small retrospective sample of infants and toddlers and can serve as an "anchor point" for clinicians encountering such patients. Limitations of the study include retrospective design, small sample size, smaller sample of risperidone usage compared to olanzapine, and use of a single and older delirium diagnostic instrument, with recent advances in instrument design such as the Pre-School Confusion Assessment Method for the ICU (psCAM-ICU) and the Cornell Assessment for Pediatric Delirium (CAPD) now available.

Take-away: Delirium occurs in infants and toddlers and may be treated with atypical antipsychotics with a reasonable expectation of efficacy and tolerability. Starting doses of olanzapine and risperidone are suggested based on observational rather than empirical data. Morbidity and mortality associated with delirium justify the cautious use of these drugs after thorough evaluation for treatable medical causes and clinical psychiatric assessment supported by validated, reliable screening instruments.

References:

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2. Silver G, Traube C, Gerber LM et al. Delirium screening anchored in child development: The Cornell Assessment for Pediatric Delirium. Palliative and Supportive Care. (2015). 13, 1005-1011.

Reviewer: John P. Glazer, M.D., Barbara Bush Children's Hospital and Division of Child & Adolescent Psychiatry, Maine Medical Center

Source: Turkel SB, Jacobson JR, Tavare CJ. The Diagnosis and Management of Delirium in Infancy. Journal of Child and Adolescent Psychopharmacology (2013) 23(5): 352-356. Pubmed link can be found here.

CLiPPs Feedback

We appreciate any feedback for our young, developing review series.

CLiPPs is edited by Chase Samsel, MD, Boston Childrens Hospital and Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA 02115. All critical summaries are written by the designated reviewers.

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