CLINICAL CASE ROUNDS IN CHILD AND ADOLESCENT PSYCHIATRY

# Nocturnal Anxiety in a Youth with Rapid-onset Obesity, Hypothalamic Dysfunction, Hypoventilation, and Autonomic Dysregulation (ROHHAD)

**Eugene Grudnikoff MD[1,2]; Carmel Foley MD[1,2]; Claudette Poole MD[2,3]; Eva Theodosiadis MD[1,2]**

## Abstract

**Objective**: Behavioral and psychiatric disorders are common in youth with rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD). We outline a rational approach to psychiatric treatment of a patient with a complex medical condition. **Methods:** We report the course of symptoms in a teen with ROHHAD, the inpatient treatment, and review current evidence for use of psychopharmacologic agents in youth with sleep and anxiety disturbances. **Results:** A 14-year-old female began rapidly gaining weight as a preschooler, developed hormonal imbalance, and mixed sleep apnea. Consultation was requested after a month of ROHHAD exacerbation, with severe anxiety, insomnia, and auditory hallucinations. Olanzapine and citalopram were helpful in controlling the symptoms. Following discharge, the patient gained weight and olanzapine was discontinued. Lorazepam was started in coordination with pulmonary service. Relevant pharmacologic considerations included risk of respiratory suppression, history of paradoxical reaction to hypnotics, hepatic isoenzyme interactions and side effects of antipsychotics. **Conclusions:** Core symptoms of ROHHAD may precipitate psychiatric disorders. A systematic evidence-based approach to psychopharmacology is necessary in the setting of psychiatric consultation.

***Key Words:*** *ROHHAD, nocturnal anxiety, insomnia*

## Résumé

**Objectif**: Les troubles comportementaux et psychiatriques sont fréquents chez les adolescents souffrant du syndrome d'obésité infantile d'installation rapide-dysfonctionnement hypothalamique-hypoventilation-dysautonomie (ROHHAD). Nous présentons une approche rationnelle de traitement psychiatrique d'une patiente souffrant d'une affection médicale complexe. **Méthodes:** Nous rendons compte de l'évolution des symptômes chez une adolescente souffrant du syndrome ROHHAD et du traitement de la patiente hospitalisée, et nous examinons les données probantes actuelles sur l'utilisation d'agents psychopharmacologiques chez les adolescents souffrant de perturbations du sommeil et d'anxiété. **Résultats:** Une adolescente de 14 ans s'est mise à prendre rapidement du poids en âge préscolaire, a développé un déséquilibre hormonal, et une apnée du sommeil mixte. Une consultation a été demandée après un mois d'exacerbation du ROHHAD, avec grave anxiété, insomnie, et hallucinations auditives. L'olanzapine et le citalopram ont aidé à contrôler les symptômes. Après son congé, la patiente a pris du poids et cessé l'olanzapine. Le lorazépam a été initié en coordination avec un service de pneumologie. Les considérations pharmacologiques pertinentes étaient notamment le risque de suppression respiratoire, les antécédents de réaction paradoxale aux hypnotiques, les interactions de l'isoenzyme hépatique, et les effets secondaires des antipsychotiques. **Conclusions:** Les symptômes de base du syndrome ROHHAD peuvent précipiter les troubles psychiatriques. Une approche systématique de la psychopharmacologie fondée sur les données probantes est nécessaire dans le contexte de la consultation psychiatrique.

***Mots clés:*** *ROHHAD, anxiété nocturne, insomnie*

[1] Department of Psychiatry, Zucker Hillside Hospital, North Shore-LIJ Health System, New York, New York, USA

[2] Hofstra School of Medicine, New York, New York, USA

[3] Department of Pediatrics Steven and Alexandra Cohen Children's Medical Center of New York, North Shore-LIJ Health System, New York, New York, USA

Corresponding E-Mail: egrudnikof@nshs.edu

Submitted: October 8, 2012; Accepted: April 14, 2013

## Background

Children with rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD) have a variable constellation of disabling symptoms, including rapid weight gain, respiratory compromise, water imbalance, and mixed sleep apnea (MSA) (Ize-Ludlow et al., 2007). Behavioral and mood disorders are common (31.4% and 15.7% of the 51 reported cases, respectively) and present a clinical challenge since little is known about the neurodevelopmental pathophysiology of the disorder (Chew, Ngu, & Keng, 2011).

## Methods

We report on the course of the psychiatric symptoms and treatments in a teen with ROHHAD. We outline important considerations involved in the treatment of anxiety and sleep disturbance in a youth with multisystemic medical illness.

## Case Report

Patient is a 14-year-old female, who had a normal course of development until the age of four. At that time she gained 9kg over four months, stopped growing linearly, developed personality changes, irritability, and physical aggression. Her sleep was plagued by nightmares and insomnia; diphenhydramine did not improve sleep. Patient required multiple surgeries, including removal of a ganglioneuroma; post-anesthesia resuscitation was invariably prolonged. Over time, patient was treated with desmopressin, growth hormone, and estrogen therapies for water imbalance, growth, and puberty delay. In her teens, patient developed severe avoidance behaviors. Anxiety and sleep symptoms were intermittent, worsening during exacerbations of autonomic and respiratory dysfunction. An attempt to treat sleep symptoms with the combinations of melatonin with zolpidem, and melatonin with eszopiclone produced paradoxical worsening of sleep and anxiety (intensifying night terrors, vivid dreams and increased distress).

The patient was admitted to pediatric inpatient unit with exacerbation of ROHHAD and one month of disabling fear of the dark and of falling asleep. She developed significant anticipatory anxiety, as well as insomnia, and nighttime auditory hallucinations (AH), a sarcastic voice stating, "You're a good girl." Extremely anxious, patient could not fall asleep for more than a few hours; she exhibited diminished ability to cope and behaviorally regressed, seeking constant reassurances and handholding. Physiological sensations related to frequent hyper- or hypothermia and bradycardia perpetuated anxiety. Poor tolerability of bi-level positive airway pressure (BiPAP) during sleep and activation of diaphragmatic pacer during periods of oxygen desaturation made deep restorative sleep rare. Cognitive "sun-downing" was noted. The family recalled that patient started estrogen therapy two months prior to admission; estrogen was discontinued after a month of treatment by the family, who believed it precipitated sleep and psychiatric deterioration.

We recommended olanzapine 2.5mg for AH and severe anxiety. Olanzapine was increased to 5mg two days later, and provided most relief when given three hours before bedtime. Citalopram 5mg was started, titrated to 15mg over five days. We offered the family psychoeducation and skills for coping with the child's chronic condition. Behavioral interventions were considered but not implemented during hospitalization.

Patient's anxiety, fears, and sleep improved, and her auditory hallucinations resolved. She was discharged home after six days of hospitalization. During her outpatient follow-up, she was noted to have gained 6lbs. within a month. Subsequently, olanzapine was discontinued. A trial of trazadone did not improve sleep. Lorazepam 1mg in the evening was started in coordination with the pulmonary service, as patient was able to tolerate nighttime diaphragmatic pacer use. Citalopram was increased to 20mg. On this regimen, and with good management of autonomic and respiratory instability, patient's insomnia, hallucinations, and anxiety remained well-controlled for six months at the time of this report.

## Case Discussion

Symptoms of mood, psychosis, and disruptive behavior disorders are described in the reports on ROHHAD (Chew, 2011), however symptoms of anxiety disorders had not been reported previously. In ROHHAD, psychiatric symptoms are commonly precipitated or exacerbated by the symptoms of the illness, particularly by the respiratory compromise (Ize-Ludlow et al., 2007).

Anxiety is uncommon in children with central hypoventilation (Pine et al., 1994); this observation is supported by the hypothesis that heightened carbon dioxide sensitivity is an important factor in anxiety pathophysiology (Pine et al., 2000). In our patient with low hypercapnea sensitivity, anxiety was exacerbated by extremely unpleasant sensations of autonomic dysfunction, as well as nightmares and anticipation of them.

### *Differential Diagnosis*

Psychiatric symptoms occurring during exacerbation of ROHHAD may remit after respiratory and hypothalamic dysfunctions are treated. Thus, psychosis and anxiety were unlikely to be primary psychiatric disorders. The diagnosis of a mental disorder due to the medical condition was better supported by patient's history and presentation. The diagnosis of substance-induced anxiety was also considered as estrogen can trigger psychotic symptoms (Kulkarnia et al., 2001).

Since sleep disturbance invariably coincided with anxiety and exacerbation of ROHHAD symptoms, the diagnosis of "insomnia related to medical condition" is likely. Anxiety

may likewise be the causative factor in patient's severe insomnia, i.e. "insomnia related to another mental disorder." This hypothesis was supported by patient's reports of fear of sleeping alone, as well as the history of paradoxical response to non-benzodiazepine hypnotics which promote sleep but lack anxiolytic properties. In the absence of causative medical and mental disorders, diagnoses of behavioral insomnia of childhood, and psychophysiological insomnia should be considered.

### *Psychopharmocologic Considerations*

Our primary goal was to provide relief from hallucinations, anxiety, and insomnia, while patient's medical condition was being stabilized by the pediatric subspecialty services. No literature was found on the treatment of psychiatric symptoms in youth with ROHHAD; therefore, we used general practice guidelines for evaluation and treatment of youth with physical illness (DeMaso, Martini, Cahen, & the Work Group on Quality Issues, 2009).

Benzodiazepines are used to treat anxiety and sleep disorders, but lack indication for pediatric insomnia. Furthermore, they may contribute to central respiratory depression in youth with MSA and central alveolar hypoventilation, and were not used during ROHHAD exacerbation. There is no evidence for their use in youth with diaphragmatic pacers.

Citalopram has no official indication for use in pediatric patients, but is nonetheless commonly prescribed to them. In treating a teen with a complex drug regimen, citalopram was selected for its favorable profile with respect to inhibition of hepatic isoenzymes. Importantly, selective serotonin reuptake inhibitors are not associated with respiratory suppression. Furthermore, the serotonergic system is implicated in modulation of anxiety, regulation of sleep-related breathing disorders (Alfano, Ginsburg, & Kingery, 2007), and speculated to be involved in pathophysiology of ROHHAD (Chew et al., 2011).

When recommending atypical antipsychotics, risks of side effects, particularly weight gain must be considered, particularly in children with primary hypothalamic dysfunction. We aimed for short-term therapy with olanzapine for relief of AH, while minimizing the risk of extrapyramidal side effects. Other antipsychotic medication options could be considered and would be appropriate, particularly if a longer course of treatment is anticipated.

## Conclusion

A systematic, evidence-based approach to evaluation and pharmacologic management is necessary in addressing psychiatric symptoms in the setting of a psychiatric consultation. Rational consideration of the pathophysiology of medical illness, psychosocial factors, and abundance of caution are imperative in recommending treatment for youth with a multi-systemic poorly understood syndrome. While ROHHAD is a rare phenomenon, our approach may be useful in treating youth with insomnia, MSA and anxiety disorders, which frequently co-occur.

## Acknowledgements/Conflicts of Interest

The authors have no financial relationships to disclose.

## References

Alfano, C. A., Ginsburg, G. S., & Kingery, J. N. (2007). Sleep-related problems among children and adolescents with anxiety disorders. *Journal of the American Academy of Child & Adolescent Psychiatry, 46*(2), 224-232.

Chew, H. B., Ngu, L. H., & Keng, W. T. (2011). Rapid-onset obesity with hypothalamic dysfunction, hypoventilation and autonomic dysregulation (ROHHAD): A case with additional features and review of literature. BMJ Case Reports.

DeMaso, D. R., Martini, D. R., Cahen, L. A., & the Work Group on Quality Issues (2009). Practice parameter for the psychiatric assessment and management of physically ill children and adolescents. *Journal of the American Academy of Child & Adolescent Psychiatry, 48*(2), 213-233.

Ize-Ludlow, D., Gray, J. A., Sperling, M. A., Berry-Kravis, E. M., Milunsky, J. M., Farooqi, I. S.,…Weese-Mayer, D. E. (2007). Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation presenting in childhood. *Pediatrics, 120*(1), e179.

Kulkarnia, J., Riedela, A., de Castella, A. R., Fitzgerald, P. B., Rolfe, T. J., Taffe, J., & Burger, H. (2001). Estrogen – A potential treatment for schizophrenia. *Schizophrenia Research, 48*(1), 137-144.

Pine, D. S., Klein, R. G., Coplan, J. D., Papp, L. A., Hoven, C. W., Martinez, J.,…Gorman, J. M. (2000). Differential carbon dioxide sensitivity in childhood anxiety disorders and nonill comparison group. *Archives of General Psychiatry, 57*(10), 960-967.

Pine, D. S., Weese-Mayer, D. E., Silvestri, J. M., Davies, M., Whitaker, A. H., & Klein, D. F. (1994). Anxiety and congenital central hypoventilation syndrome. *American Journal of Psychiatry, 151*, 864-870.