Improved Behavior and Neuropsychological Function in Children With ROHHAD After High-Dose Cyclophosphamide

Lisa A. Jacobson, PhD,[a,b] Shruti Rane, PhD,[a] Lisa J. McReynolds, MD, PhD,[c] Diana A. Steppan, MD,[c] Allen R. Chen, MD, PhD, MHS,[c] Ido Paz-Priel, MD[c]

abstract

Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD) is a rare, generally progressive, and potentially fatal syndrome of unclear etiology. The syndrome is characterized by normal development followed by a sudden, rapid hyperphagic weight gain beginning during the preschool period, hypothalamic dysfunction, and central hypoventilation, and is often accompanied by personality changes and developmental regression, leading to substantial morbidity and mortality. We describe 2 children who had symptomatic and neuropsychological improvement after high-dose cyclophosphamide treatment. Our experience supports an autoimmune pathogenesis and provides the first neuropsychological profile of patients with rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation.

Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD) is characterized by normal development followed by a sudden, rapid hyperphagic weight gain beginning during the preschool period, hypothalamic dysfunction, and central hypoventilation.[1–3] Without intervention, symptoms progress leading to substantial morbidity and mortality.[1–3] In addition, these patients display poorly characterized mood disorders, personality changes, and developmental regression, including loss of toilet-training, and behavior mimicking autism spectrum disorders.[1,2,4–6]

The etiology of ROHHAD is unknown and careful investigations have not revealed a genetic etiology.[2,7–9] The association with neural crest tumors suggests an immune-mediated process resembling opsoclonus myoclonus ataxia syndrome.[2,5,7,10] Lymphocytic infiltration of the brain,[11,12] presence of oligoclonal bands in the cerebrospinal fluid,[13] and response to immunomodulary therapy[5,14] support an autoimmune process.

High-dose cyclophosphamide (Hi-Cy) results in near total ablation of active lymphocytes without myeloablation, thereby "rebooting" the immune system, making it an efficacious and safe approach for selected patients with severe refractory autoimmune diseases.[5,15] We previously reported on a child with ROHHAD whose symptoms improved after Hi-Cy.[5] We now describe serial neuropsychological assessments of 2 consecutive, similarly treated

[a]Department of Neuropsychology, Kennedy Krieger Institute, Baltimore, Maryland; and [b]Department of Psychiatry and Behavioral Sciences, and [c]Division of Pediatric Oncology, Johns Hopkins University School of Medicine, Baltimore, Maryland

Dr Jacobson collected the data, was responsible for the original idea and the development of the manuscript, conducted analysis, and drafted, reviewed, and revised the manuscript; Dr Rane collected the data and critically reviewed and revised the manuscript; Drs McReynolds and Steppan collected the data and critically reviewed and revised the manuscript; Dr Chen was responsible for the original idea of the manuscript, collected the data, and critically reviewed the manuscript; and Dr Paz-Priel was responsible for the original idea and the development of the manuscript, collected the data, conducted analysis, and drafted, reviewed, and revised the manuscript.

This trial has been registered at www.clinicaltrials.gov (identifier NCT02441491).

Dr Paz-Priel's current affiliation is Genentech, Inc., South San Francisco, CA.

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Addresss correspondence to Lisa A. Jacobson, PhD, Department of Neuropsychology, Kennedy Krieger Institute, 1750 East Fairmount Ave, Baltimore, MD 21231. E-mail: jacobson@kennedykrieger.org

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ROHHAD patients demonstrating the socioemotional changes after onset of weight gain, lack of intellectual disability as part of the ROHHAD phenotype, and a response to Hi-Cy treatment that, consistent with improvement in other symptoms, persisted for >12 months of follow-up.

CASES DESCRIPTION

Case 1

A 26-month-old girl developed hyperphagia, with weight increasing from 16.8 to 35.5 kg at age 36 months. Evaluation at 43 months did not reveal autonomic dysfunction or central hypoventilation. At age 45 months, a ganglioneuroblastoma was resected requiring no additional treatment. In addition, she developed partial diabetes insipidus, social withdrawal, reduced pain perception, strabismus, and intermittent papular rash. Therefore, the diagnosis of ROHHAD was made. At diagnosis, BMI was 39.5 (Z-Score +3.65) and a sleep study showed saturation nadir of 84% with end tidal carbon dioxide >50 mm Hg during 85% of total sleep time.

At age 55 months, the patient received 5 weekly doses of rituximab (375 mg/m^2/dose[5]) resulting in transiently improved hyperphagia, social skills, and pain perception. She then received cyclophosphamide (50 mg/kg ideal weight/day) on 4 consecutive days.[5] Therapy was well tolerated with a 4-day uncomplicated neutropenia. Over the ensuing months, she developed chylothorax that spontaneously resolved and started on Adderall (amphetamine and dextroamphetamine), which may have facilitated weight loss. At 18 months post–Hi-Cy, parents reported markedly diminished hyperphagia, resolution of aggressive food-seeking behavior,

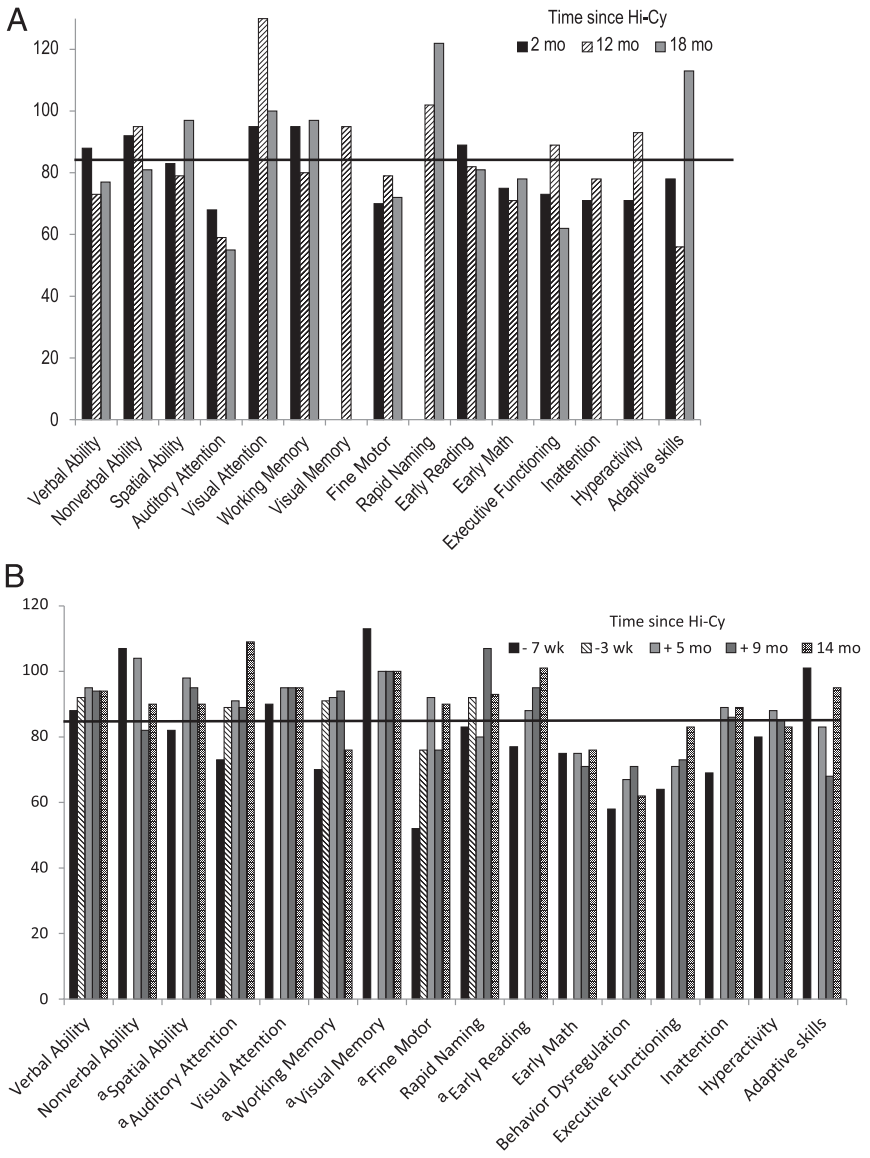

FIGURE 1
Results of serial neuropsychological assessments. Performance of patient 1 (A) or patient 2 (B) by neuropsychological domain is shown at the indicated time points in relation to Hi-Cy treatment. The horizontal line marks 1 SD below the mean for age. [a]Reliable change index (RCI)[17] from baseline.

normalization of pain perception, and markedly improved empathy with appropriate emotional responses. Accordingly, her modified autism impact measure ([AIM] range, 18–90)[16] score improved from 49 to 85. BMI declined to 30 (Z-Score +2.9), and a sleep study demonstrated average oxygen saturation of 95%, nadir of 91%, and no episodes of end tidal carbon dioxide >50 mm Hg. Figure 1A presents the results of neuropsychological evaluations performed at 2 and 12 months post–Hi-Cy. Supplemental Table 1 details the neuropsychological tests used.

Case 2

A 30-month-old boy presented with hyperphagia and 18-kg weight gain over 3 months. He subsequently developed behavioral changes with detached nonempathetic personality, unprovoked profuse sweating, temperature instability with spikes to 38.5°C, strabismus,

hyperprolactinemia, loss of toilet-training, reduced pain sensation, and debilitating bipedal neuropathic pain. At age 6.7 years, BMI was 33.7 (Z-Score +3.10), and a sleep study revealed central apnea (1.5/hour) and hypopnea (13.3/hour), with saturation nadir of 87%. A course of rituximab[5] resulted in temporary normalization of appetite and temperature instability, reduced enuresis, and improved neuropathic pain, sweating, and interpersonal skills. Interestingly, a transient improvement in attentional regulation was also seen after rituximab therapy (Supplemental Table 1). Next, he received Hi-Cy,[5] which he tolerated well with a brief, uncomplicated neutropenia.

The results of serial neuropsychological evaluations, by domain, are presented in Fig 1B. On evaluation 10 months after Hi-Cy, BMI declined to 32.4 (Z-Score +2.81), and, as observed by parents and clinic staff, he showed reduced hyperphagia, improved neuropathic pain and pain sensitivity, and resolution of temperature instability and diffuse perspiration. However, his constipation and hyperprolactinemia did not resolve. At 15 months after Hi-Cy, BMI was 35.6 kg/m^2 (Z-Score +2.80). Sleep studies at 10 and 15 months post–Hi-Cy showed improvement in central apnea (0.6/hour and 0.8/hour, respectively) and hypopnea (9.4/hour and 8.9/hour, respectively), with saturation nadir still at 86%. The markedly improved behavior and social interactions, as reported by parents and observed during assessment appointments by clinicians, were reflected by a modified AIM[16] score increase from 41 to 60.

The parents of both patients gave informed consents for this report.

DISCUSSION

To our knowledge, this is the first report of neuropsychological characterization of children with ROHHAD. Emergence of ROHHAD symptoms was associated with reduced social reciprocity, flattened affect, increased rigidity/inflexibility, reduced interest in social interactions, and limited demonstrations of affection with caregivers. Assessment of both patients showed perseverative behavior, reduced flexibility, and anxiety, with notable improvement after treatment. This neuropsychological pattern appears similar to that seen in autism spectrum disorders, including apparent regression in skills after onset of ROHHAD symptoms. Although the affective and social symptoms associated with ROHHAD did not remit entirely, we observed measurable improvements after Hi-Cy. As indicated by parental reports and AIM scores, both patients showed greater interest in peer interactions, affection toward caregivers, and improved behavioral rigidity. This is a functionally significant improvement that allows our patients to regain social interactions with family and peers and participate in regular school settings.

Both patients had variable cognitive function, with important abilities within the normal range for age (above –1 SD), including nonverbal reasoning abilities, visual attention, working memory, and visual memory. Both patients demonstrated weaknesses in early math conceptual understanding, with preserved reading-related skills. Overall, neither patient met criteria for intellectual disability. Neuropsychological evaluation of patient 1 was limited by significant anxiety and selective mutism and by initial assessment 2 months after Hi-Cy, when fully recovered from therapy. However, these factors may potentially cause an underestimation of the benefit of therapy.

Parent report indicated both children showed stability or improvements in attentional regulation as well as increased social interest and reciprocal interactions after Hi-Cy. Of 11 neuropsychological domains in which initial functioning was >1 SD below average, 7 improved to within normal limits after rituximab and/or Hi-Cy. Improvements were sustained throughout follow-up (now >14 months after treatment). Specifically, functional improvements in inattentive and dysexecutive symptoms resulted in normalization of auditory attention span and a drop to subthreshold levels of attention-deficit/hyperactivity disorder (ADHD) symptomatology postrituximab for patient 2 and post–Hi-Cy for both. These improvements, coupled with behavioral support, allowed normalization of adaptive skills by the final evaluation.

Consistent with our previous experience,[5] both patients had clinically meaningful improvement of symptoms, and importantly, neither had deterioration over 14 to 18 months of follow-up. Stability of improvement in BMI may have been at least partially attributable to Adderall in case 1, although improvement over the initial year post–Hi-Cy was noted in case 2. Lack of complete symptom resolution is likely owing to an irreversible injury. Our patients were treated 2.5 or 4.5 years from onset of symptoms, and early treatment may yield better response, as noted in other immune-mediated neurologic diseases.[18] As an immune-mediated neurologic syndrome, a variable phenotype may be expected.[1,7] Both patients demonstrated salient features of ROHHAD, including rapid-onset weight gain after normal early development, autonomic dysregulation, ganglioneuroblastoma, and hypothalamic dysfunction. A lack of hypoventilation may not necessarily exclude ROHHAD,

because this is a late symptom whose incidence might be overestimated by its inclusion in case definitions of previous reports and by a diagnosis bias of patients with severe respiratory compromise. Indeed, Bougneres et al[1] reported that only 1 of 6 patients with ROHHAD had hypoventilation by age 6. Although limited, our institutional experience (comprised of the currently described cases and 1 previous report[5]) suggests that intensive immunosuppression benefits selected patients with ROHHAD, an otherwise devastating and potentially fatal condition, and a prospective clinical trial is underway (www.clinicaltrial.gov, identifier NCT02441491).

ABBREVIATIONS

AIM: autism impact measure
Hi-Cy: high-dose cyclophosphamide
ROHHAD: rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation

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