# Growth hormone treatments and cognitive functioning in children with Prader–Willi syndrome

**Cheri L Deal**[1] and **Alan D Rogol**[2]

[1]Endocrine and Diabetes Service, CHU-Ste-Justine, Sainte-Justine Hospital, Montreal, Quebec, Canada and [2]University of Virginia, Charlottesville, Virginia, USA

Correspondence should be addressed to A D Rogol
**Email**
adrogol@comcast.net

European Journal of Endocrinology

The article by Donze *et al.*, in a recent issue of EJE (1), concludes that prompt initiation of rhGH treatment of infants with Prader–Willi Syndrome (PWS) permits the development of cognition (as measured by IQ) at the same *pace* as healthy peers. Up until this century, the Prader–Willi (aka Prader–Labhart–Willi) syndrome (OMIM #176270) was a little known, rare genetic condition among endocrinologists other than being part of their differential diagnosis of obesity.

PWS is a multisystem, genetically heterogeneous condition caused by a lack of paternal gene expression at the chromosome 15q11–q13 PWS locus and is one of many syndromes which has helped us to further understand the importance of epigenetics to gene expression. Its birth incidence estimates have increased over time as genetic testing has moved to DNA methylation analysis as the primary test, and it is currently thought to be approximately 1:15 000 live births (2).

The clinical phenotype changes over time, from prenatal followed by post-natal hypotonia, whose clinical course can be modified to some degree by current medical treatment coupled with multidisciplinary interventions (2). Initially, the hypotonia is accompanied by feeding difficulties and failure to thrive in early infancy, often requiring assisted feeding. Appetite and food-related behavior subsequently evolve through several distinct phases, culminating in extreme hyperphagia and abnormal food-seeking behavior that can include stealing, eating from garbage cans, and throwing tantrums if denied food access (2). Excessive food intake and severe obesity occur over time, putting them at high risk for obesity-related comorbidities; a very few individuals may be capable of controlling appetite as young adults.

Body composition is characterized by an increased fat mass and a decreased lean body mass even in infancy, before obesity is evident. By the ages between 2 and 5, caloric needs are also far less than the Recommended Dietary Allowance (RDA) for this age group because of the decreased basal metabolic rate in these individuals and need to be decreased to 60–80% to prevent evolving obesity. The dysregulation of the hypothalamus extends beyond hyperphagia and basal metabolic rate and may include hormone deficiencies. Hypogonadism is present in the vast majority of patients and may be a mixture of primary and central, at least in boys. It may manifest as small external genitalia, undescended testes, and later absent or incomplete pubertal maturation. In girls, the genital hypoplasia may be more subtle as a small clitoris or labia, especially the labia minora; fertility has rarely been documented in women (2). GH deficiency can often be demonstrated and explains at least a part of the body composition abnormalities as well as the short adult stature; however, one should recognize that the peak GH level for most growth hormone stimulation tests is lower for the obese and super-obese, making it difficult to determine sensitive and specific cut-off values. IGF-I levels are also lower than expected in children with PWS for the degree of obesity, likely because of their lower insulin levels. Cessation of rhGH therapy at the end of linear growth results in a deterioration of body composition, and studies are still necessary to evaluate longer-term use of GH in this population (2). It is reassuring, therefore,

https://eje.bioscientifica.com
https://doi.org/10.1530/EJE-20-0222

Published by Bioscientifica Ltd.

that GH treatment does not contribute to type 2 diabetes in the absence of obesity (3). Central hypothyroidism and ACTH deficiency occur, but the literature has disparate numbers for their prevalence, without consensus. Interestingly, these patients show very early adrenarche; increases in DHEA-S concentrations occur in children with PWS as young as at the age of 4 (2). This probably contributes to their more rapid bone age advancement and earlier attainment of adult height.

By far the most difficult aspect of the evolving phenotype, however, is that of the behavioral manifestations, which include increased oppositional and aggressive behavior, mood lability, temper outbursts, auto-mutilation (skin-picking), anxiety, and obsessive-compulsive traits. It is also increasingly apparent that a large percentage of patients, particularly those with chromosome 15 uniparental disomy (UPD), will eventually manifest psychotic behavior (4).

In the past, our ability to diagnose children with this syndrome was based on recognition of the typical dysmorphic features and relied on fluorescent *in situ* hybridization (FISH) analysis to demonstrate a deletion in the PWS locus. This often led to delays in diagnosis, as the molecular genetics are now known to not only include two major sizes of deletion on the paternal chromosome 15q11–13, but also to include individuals with maternal uniparental disomy or, much less commonly, chromosomal rearrangements leading to smaller deletions or defects in the imprinting process by itself. Although the vast majority of children with PWS represent sporadic inheritance, rare familial cases have been reported in conjunction with very small deletions of the imprinting control center, which is responsible for determining which genes, maternal or paternal, will be actively transcribed. This genetic diversity in pathophysiology presents particular diagnostic and counseling challenges (2). The potential link of PWS syndrome with epigenetic errors possibly because of assisted reproduction technology involving intracytoplasmic sperm injection (ICSI) has alerted physicians to be attentive to reproductive history of the parents when a new child has been diagnosed with PWS (5). Understanding the molecular basis for Prader–Willi Syndrome also permits more detailed studies on genotype-phenotype relationships and, as recently noted, this is perhaps critical in predicting the neuropsychological and psychiatric manifestations of individuals living with this condition. These issues as well as those related to excessive eating and morbid obesity have been reviewed in depth (2, 6, 7).

Virtually, all major developmental milestones, including fine and gross motor skills and language development are delayed. Cognitive deficits range from mild to more severe, although the implementation of multidisciplinary teams over the last 15–20 years has markedly changed the landscape of the 'typical' child with PWS seen in the more distant past. All recent clinical practice recommendations recognize the importance of early stimulation and rapid prevention or treatment of comorbidities frequently seen such as sleep apnea, dental issues, and scoliosis, to name only a few.

Growth hormone administration has also been widely felt to be a cornerstone of treatment of children with PWS (8). It was approved by the US Food and Drug Administration (FDA) based on the stimulation of height velocity and by the European Medicines Agency (EMA) based on improvements in both height velocity and body composition. When prescribed in slightly supraphysiologic doses during childhood, it has shown benefits not only on adult height, but also on the maintenance of an average BMI in the range of +2.5 SDS and an adequate bone mineral density. In patients treated with rhGH, both before and after the initiation of replacement therapy with sex hormones, additional benefits can be seen in muscle mass, strength, VO2max, endurance, bone mineral density, quality of life measures, and decrease in fat mass.

In their report, Donze and co-workers note the cognitive effects of rhGH treatment of infants and children with PWS (1). Potential mechanisms for its effects on cognition have been reviewed and supported by animal and *in vitro* data (4). The data presented in this issue extends their previous data and those of other groups, as noted in their reference list, obtained over shorter periods than the present 8-year study. The early studies included a placebo control and noted that children with PWS treated with rhGH for 2 years developed at the same trajectory as a healthy reference population, but the control group noted significant deterioration (1). Primarily, because of these data, all children in the Netherlands are now treated with rhGH at an early age and parents of children with PWS on several continents are actively seeking GH treatment soon after the birth of their child. This clearly limits our potential to design confirmatory, long-term placebo-controlled studies.

In this 8-year longitudinal, prospective study, the investigators evaluated the effects of continuous treatment with rhGH from infancy. A second group which received rhGH beginning only later in childhood (~8 years) was

included to determine if an early start of rhGH therapy was beneficial in the longer term.

Forty-three children with genetically confirmed diagnosis of PWS who were naive to rhGH and had at least three WISC tests during the 8 years of follow-up were evaluated. The second phase included a cross-sectional cohort of 22 children with PWS who began therapy in infancy and were compared to the 43 longitudinally studied children who started rhGH therapy later in childhood. Cognitive function was assessed using the WISC, suitable for children 6 to 16 years of age. Three subtests, Block Design, Vocabulary, and Similarities, were administered. At baseline, those who started rhGH therapy at a median age of 8.1 years had an estimated mean block design score below −2 s.d. for the Dutch reference population without PWS, but the Vocabulary and Similarities tests were within the normal range. The estimated total IQ score was consistent with mild intellectual impairment. During the 8-year period of therapy with rhGH, the subtest scores did not change significantly, demonstrating no deterioration in visual spatial skills, abstract verbal reasoning, or vocabulary skills. Thus, the children with PWS developed at the same trajectory as the reference population.

The effect of age at start of therapy was evaluated in a separate group of 22 children with PWS and compared to those of the 43 longitudinally investigated children who began therapy later in childhood. Although those who began in infancy had a significantly greater vocabulary score and estimated total IQ, scores in the other two subtests were indistinguishable. The results of this last comparison did not account for a number of possible differences (confounders) between the groups that are known to affect the cognitive trajectories of children and thus could affect the results: the activity and motor benefits of rhGH therapy that give the children more energy and the ability to explore their environment at an earlier, critical age; the educational level and IQ of the parents and their socioeconomic status; the incidence of maternal depression; and the number of contacts with the multidisciplinary team members compared to those starting GH at a later age (6, 9). The investigators rightly note no deterioration in some skills that might have been expected from their earlier randomized, control trial with rhGH vs no additional treatment. Thus the children with PWS were developing at a rate similar to the healthy Dutch population (controls), albeit at a lower level.

It may also be that earlier and more aggressive use of GH therapy in these infants also prevents previously undocumented episodes of hypoglycemia. Given the recent understanding of how defects in *MAGEL2*, an imprinted gene lying within the PWS locus, can result in episodes of hypoglycemia which resolve with GH therapy (10) as well as the abnormal counter regulatory responses to hypoglycemia observed in Magel2-null mice (11), we should not exclude unrecognized hypoglycemia as a contributor to the cognitive delay in PWS.

It is our view that the even more important issues that require attention are the food-seeking behavior and the other behavioral aspects of this syndrome, such as the repetitive behaviors as well as the difficulties with social interactions and the long-term risk for psychiatric disease. These can markedly affect the quality of life of the caregivers (12, 13, 14, 15).

There are currently a large number of investigational drugs under study which target hyperphagia and obesity (16). Drug development is not without its challenges, as in the case of the hyperphagia target compound, methionine aminopeptidase 2 inhibitor. Phase 3 trials were halted because of serious adverse events (pulmonary thrombo-embolism). We have, since, acquired better epidemiologic data evaluating morbidity and mortality in patients with PWS, which will result in better trial design and surveillance, since thrombosis is an already anticipated event in the very obese patient with PWS (17). It is hoped that the use of a validated hyperphagia questionnaire for PWS (18) will help to objectify drug responsiveness, in as much as the caregivers are able to accurately assess abnormal food-seeking behavior. This is difficult when there is a very strict control on food access, particularly, as older adolescents become better at manipulation. Caregivers are also desperate to find a solution to their child's hunger and may therefore use a longer recall period than stipulated by protocol. One promising therapy, among others, includes LV-101 (carbetocin) administered intra-nasally, because it may not only target hyperphagia, but also some of the anxiety manifestations and the repetitive behaviors. This oxytocin analog has shown positive results in phase 2 trials (18). The ultimate solution may be a combination of pharmaco/therapeutic approaches similar to what has been used in other fields when the pathophysiology is polygenic and heterogeneous.

As mentioned previously, the high risk of psychosis and other psychiatric comorbidities in this population is perhaps one of the most concerning observations, and higher levels of cognition may not be protective (6, 7). These comorbidities not only require a better understanding of their similarities and differences

compared to the population without PWS, but it should stimulate us to make concerted efforts to diagnose, treat, and perhaps someday even prevent them (2).

In conclusion, it may be a rather long leap – from rhGH stimulating its receptor throughout the brain and GH/IGF-1 affecting the genesis of neurons stimulating brain growth, development and myelination – to an improvement in IQ in PWS, and we must be careful in the messages we convey to the community of families living with a child recently diagnosed with PWS. The factors influencing the developmental trajectories of IQ are complex, and we now understand that IQ is no longer static (19). It is far more complex, beginning with the genetics of parental IQ beyond the PWS locus, the genetic subtype of PWS, and the marked evolution in how these children are now integrated into health networks – particularly in countries with universal healthcare where socioeconomic status (SES) of the families may play a lesser, but non-negligent, role as an environmental confounder. The multidisciplinary approach to the care of patients with PWS is now more proactive and anticipatory, and team members see the children frequently. Earlier use of rhGH may help infants not only to better interact with their environment through improvement in lean body mass and endurance, but also because it means increased contact with families, allowing for improved support of the caregivers. All of this has probably contributed to the IQ trajectory in not only the children involved in the study of Donze *et al*. (1), but in all our children diagnosed with PWS in the last 15 years. A study to test this, however, is virtually impossible to design and execute, in part, because of the rare disease context, patient and family heterogeneity, and parental desire to do whatever possible to help their children. It behooves us to maintain equipoise, as we remain highly attentive to the perceptions and needs of the caregivers, as well as those of our patients living with PWS.

**Declaration of interest**

A D R had been a consultant to Zafgen, Inc. C L D had been a consultant to Zafgen, Inc. and consults for MillEndo Therapeutics and LEVO.

**Funding**

This research did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

**Author contribution statement**

Both authors contributed to the outline of the article, its several revisions, and then to the multiple versions of the full article, including the present one.

## References

1 Donze SH, Damen L, Mahabier EF & Hokken-Koelega ACS. Cognitive functioning in children with Prader-Willi syndrome during 8 years of growth hormone treatment. *European Journal of Endocrinology* 2020 **182** 405–411. (https://doi.org/10.1530/EJE-19-0479).

2 Butler MG, Miller JL & Forster JL. Prader-Willi syndrome – clinical genetics, diagnosis and treatment approaches: an update. *Current Pediatric Reviews* 2019 **15** 207–244. (https://doi.org/10.2174/1573396315666190716120925)

3 Crino A & Grugni G. Update on diabetes mellitus and glucose metabolism alterations in Prader-Willi syndrome. *Current Diabetes Reports* 2020 **20** 7. (https://doi.org/10.1007/s11892-020-1284-5)

4 Nyberg F & Hallberg M. Growth hormone and cognitive function. *Nature Reviews: Endocrinology* 2013 **9** 357–365. (https://doi.org/10.1038/nrendo.2013.78)

5 Hattori H, Hiura H, Kitamura A, Miyauchi N, Kobayashi N, Takahashi S, Okae H, Kyono K, Kagami M, Ogata T *et al*. Association of four imprinting disorders and ART. *Clinical Epigenetics* 2019 **11** 21. (https://doi.org/10.1186/s13148-019-0623-3)

6 Whittington J & Holland A. Cognition in people with Prader-Willi syndrome: insights into genetic influences on cognitive and social development. *Neuroscience and Biobehavioral Reviews* 2017 **72** 153–167. (https://doi.org/10.1016/j.neubiorev.2016.09.013)

7 Aman LCS, Manning KE, Whittington JE & Holland AJ. Mechanistic insights into the genetics of affective psychosis from Prader-Willi syndrome. *Lancet Psychiatry* 2018 **5** 370–378. (https://doi.org/10.1016/S2215-0366(18)30009-9)

8 Deal CL, Tony M, Hoybye C, Allen DB, Tauber M, Christiansen JS & 2011 Growth Hormone in Prader-Willi Syndrome Clinical Care Guidelines Workshop Participants. Growth Hormone Research Society Workshop Summary: consensus guidelines for recombinant human growth hormone therapy in Prader-Willi syndrome. *Journal of Clinical Endocrinology and Metabolism* 2013 **98** E1072–E1087. (https://doi.org/10.1210/jc.2012-3888)

9 Walker SP, Wachs TD, Grantham-McGregor S, Black MM, Nelson CA, Huffman SL, Baker-Henningham H, Chang SM, Hamadani JD, Lozoff B *et al*. Inequality in early childhood: risk and protective factors for early child development. *Lancet* 2011 **378** 1325–1338. (https://doi.org/10.1016/S0140-6736(11)60555-2)

10 Jobling R, Stavropoulos DJ, Marshall CR, Cytrynbaum C, Axford MM, Londero V, Moalem S, Orr J, Rossignol F, Lopes FD *et al*. Chitayat-Hall and Schaaf-Yang syndromes: a common aetiology: expanding the phenotype of *MAGEL-2*-related disorders. *Journal of Medical Genetics* 2018 **55** 316–321. (https://doi.org/10.1136/jmedgenet-2017-105222)

11 Tennese AA & Wevrick R. Impaired hypothalamic regulation of endocrine function and delayed counterregulatory response to hypoglycemia in Magel2-null mice. *Endocrinology* 2011 **152** 967–978. (https://doi.org/10.1210/en.2010-0709)

12 Ihara H, Ogata H, Sayama M, Kato A, Gito M, Murakami N, Kido Y & Nagai T. QoL in caregivers of Japanese patients with Prader-Willi syndrome with reverence to age and genotype. *American Journal of Medical Genetics: Part A* 2014 **164A** 2226–2231. (https://doi.org/10.1002/ajmg.a.36634)

13 Kayadjanian N, Schwartz L, Farrar E, Comtois KA & Strong TV. High levels of caregiver burden in Prader-Willi syndrome. *PLoS ONE* 2018 **13** e0194655. (https://doi.org/10.1371/journal.pone.0194655)

14 Mao SJ, Shen J, Xu F & Zou CC. Quality of life in caregivers of young children with Prader-Willi syndrome. *World Journal of Pediatrics* 2019 **15** 506–510. (https://doi.org/10.1007/s12519-019-00311-w)

15 Mackay J, McCallum Z, Ambler GR, Vora K, Nixon G, Bergman P, Shields N, Milner K, Kapur N, Crock P *et al*. Requirements for improving health and well-being of children with Prader-Willi syndrome and their families. *Journal of Paediatrics and Child Health* 2019 **55** 1029–1037. (https://doi.org/10.1111/jpc.14546)

16 Tan Q, Orsso CE, Deehan EC, Triador L, Field CJ, Tun HM, Han JC, Muller TD & Haqq AM. Current and emerging therapies for

managing hyperphagia and obesity in Prader-Willi syndrome: a narrative review. *Obesity Reviews* 2019 **21** e12992. (doi:10.1111/obr.12992)

17 Pacoricona-Alfaro DL, Lemoine P, Ehlinger V, Molinas C, Diene G, Valette M, Pinto G, Coupaye M, Poitou-Bernert C, Thuilleaux D *et al*. Causes of death in Prader–Willi syndrome: lessons from 11 years' experience of a national reference center. *Orphanet Journal of Rare Diseases* 2019 **14** 238. (https://doi.org/10.1186/s13023-019-1214-2)

18 Dykens EM, Miller J, Angulo M, Roof E, Reidy M, Hatoum HT, Willey R, Bolton G & Korner P. Intranasal carbetocin reduces hyperphagia in individuals with Prader-Willi syndrome. *JCI Insight* 2018 **3** e98333. (https://doi.org/10.1172/jci.insight.98333)

19 Rinaldi L & Karmiloff-Smith A. Intelligence as a developing function: a neuroconstructivist approach. *Journal of Intelligence* 2017 **5** 18. (https://doi.org/10.3390/jintelligence5020018)

Received 12 March 2020
Revised version received 27 March 2020
Accepted 1 April 2020