

## Paediatric Cushing's disease

Cushing's syndrome in childhood differs in a number of ways from the condition seen in adult patients, as Constantine Stratakis describes.



Constantine Stratakis

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*Symptoms that are less commonly seen in children include sleep disruption, mental changes and muscle weakness”*

By far the most common type of Cushing's syndrome has an exogenous cause, such as medication.<sup>1</sup> Endogenous causes are rare; they are all associated with a tumour of one form or another. For pre-pubertal children, and certainly for toddlers, the adrenals are more commonly the cause of endogenous Cushing's syndrome, whereas pituitary tumours are more often to blame in older children. Ectopic sources of Cushing's syndrome (a site other than the pituitary or adrenal) are extremely rare in children. Overall, there is a female to male predominance, which decreases with younger age. Cushing's disease refers to disease caused by pituitary adenomas only.

### Presentation of Cushing's disease

The single most important symptom, shared by almost every patient with Cushing's disease, is weight gain. Fat accumulation leads to glucose intolerance and, depending on the body's individual predisposition, diabetes, which further exacerbates the vicious cycle of fat accumulation, increased insulin levels and insulin resistance, and (due to the rise in insulin but also due to excess cortisol directly) increased appetite.

### Differences between children and adults

It is common for children with Cushing's disease to show an increase in rate of weight gain accompanied by a decrease in growth rate (linear height), due to decreased growth hormone (GH) secretion. This is often easily detected in the growth charts of children with Cushing's syndrome. Other symptoms include rounded face, reddened cheeks, acne, headache, excess hair growth (fine downy hair on cheeks, arms and legs), purplish-pink stretch marks (more common in older children), darkened skin around neck and armpit areas, easy bruising, development of pubic hair at a younger age than usual, irregular or absent menstrual periods and high blood pressure.

Compared with adults with Cushing's syndrome, symptoms that are less commonly seen in children include sleep disruption, mental changes and muscle weakness. Although many adults with Cushing's syndrome report a change in mental status that affects their job performance, children with the syndrome do not usually report problems in school performance, until, interestingly, after surgery.

### Diagnosing Cushing's disease in children

A review of the child's growth chart is essential. If the growth chart shows an increase in the rate of weight gain and a decrease in the rate of linear growth (height velocity) over the same time period, then further evaluation and monitoring are needed to determine the cause. Other diagnostic testing in children with Cushing's disease is similar to that in adults.

### Treating Cushing's disease

Pituitary adenomas are usually removed by transsphenoidal surgery. Due to the highly specialised nature of this surgery, referral to a neurosurgeon who is experienced in this procedure is recommended.<sup>2</sup> In some patients, treatment with one or more medications that control or block cortisol production may be given on a short term basis. In patients where surgery has failed (or if they were not good candidates for surgery, which is very rare in children but more frequent in adults), radiation therapy is indicated.

Various studies report that, a year after surgical cure of paediatric Cushing's syndrome, most children had lost weight and body mass and their height and growth velocity had increased.<sup>3</sup> However, final adult height is often impaired (by at least an inch (25mm)).

Many children and adolescents recovering from Cushing's disease experience changes in cognitive performance that can be stressful for both the child and the parents.<sup>4</sup> The brain is affected by prolonged exposure to abnormally high cortisol levels and, once the cortisol levels are normalised, there is a period of readjustment. Symptoms reported by some children and adolescents include difficulty concentrating and problems with memory that may affect their academic performance for an indeterminate period. It is important to provide appropriate educational and psychological resources for the child or adolescent during this period. Adult patients, especially young adults, experience mood changes too, and their overall sense of well-being is affected, even years after treatment and cure.

### Genetics of Cushing's disease

We have identified several hereditary diseases associated with genetic predisposition to the development of Cushing's disease (multiple endocrine neoplasia types 1 and 4, McCune-Albright syndrome, Carney complex, succinate dehydrogenase mutations and others). It is expected that more genes or other genetic factors will be identified, which may lead to better and targeted medical treatments.<sup>5</sup>

### Conclusion

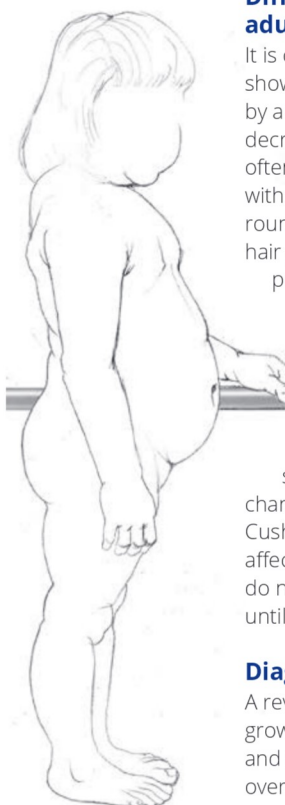
There have been significant improvements in both testing and imaging over the last 20 years in the diagnosis of Cushing's disease. These include better magnetic resonance imaging and higher specificity cortisol assays. Our understanding of effects on immunity and other systems has also increased.<sup>6</sup> But more needs to be done, especially in detecting small tumours of the pituitary gland.

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### References

1. Fleseriu et al. 2021 *Lancet Diabetes & Endocrinology* **9** 847–875.
2. Tatsi et al. 2021 *Clinical Endocrinology* **95** 856–886.
3. Valdés et al. 2021 *European Journal of Endocrinology* **184** 179–187.
4. Keil et al. 2022 *Clinical Endocrinology* **96** 569–577.
5. Tatsi et al. 2020 *Best Practice & Research: Clinical Endocrinology & Metabolism* **34** 101418.
6. Hwang et al. 2022 *Journal of Allergy & Clinical Immunology* **149** 302–314.



Typical body shape of a paediatric patient with Cushing's syndrome.

Constantine Stratakis will talk on 'Paediatric Cushing's disease' at ESPE 2022 (see page 9).