plete. Patients usually present with catabolic syndrome, hyperglycemia, hypertension, thromboembolic events and hypokalemia. The presented case showed only hypokalemia with normal-low glucose levels and blood pressure in within the range. Moreover, she had hirsutism and increased libido due to androgen secretion.

Here we report a case of a rare presentation of cortisol and androgen secretory ACC, with ulcer and upper gastrointestinal bleeding. Interestingly, earlier reports associated CS with peptic ulcer disease especially in the presence of concomitant infection with Helicobacter pylori or nonsteroidal anti-inflammatory drugs use.[5,6] More recent evidence showed that probably neither exogenous nor endogenous corticosteroid excess directly causes peptic ulcer or Helicobacter pylori infection, with even higher mortality.[7,8] Hypercortisolism may be associated with painless peptic ulcer disease with delayed ulcer healing, which potentially results in serious gastro-intestinal complications.[9]

More intriguingly, hypercortisolism induce a prothrombotic state that last even after cure of the CS[10] by altering coagulation factors, fibrinolysis and potentially increasing the platelet account.

To the best of our knowledge this is the first report of an ACC associated with CS and hyperandrogenism that was presented as an upper gastrointestinal bleeding. It is very probable that besides hypercortisolism, the combination of other factors like the use of even prophylactic dose of ASA, the chronic inflammation of the gastric wall due to the tumoral infiltration and the infection with Helicobacter pylori contributed to the upper intestinal hemorrhage.

This case illustrates the importance of the differential endocrine diagnosis in hypokalemia and moreover indicates that untreated hypercortisolism is not extent from acute hemorrhagic complications. Therefore, we considered appropriate to report it to carry out an earlier diagnostic and treatment.

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https://doi.org/10.1016/j.endinu.2021.12.006

Experience in diagnosis and treatment of prolactinomas in pediatric patients and young adults

Experiencia en el diagnóstico y tratamiento de prolactinomas en pacientes pediátricos y adultos jóvenes

Dear Editor,

Pituitary adenomas are rare in childhood, with an approximate incidence of 0.1 cases per million children, of which around 50% are prolactinomas. The associated clinical signs and symptoms are associated with age, mass effect, hyperprolactinaemia and secondary hormone deficiency. Dopamine agonists are the medical treatment of choice.[1] These usually achieve a significant reduction in tumour size, normalisation of prolactin blood levels and gonadal axis recovery in most patients.[2]

A retrospective review of patients under 21 years diagnosed with prolactin-producing adenoma (prolactinoma) in a tertiary hospital was conducted within the last six years. Patients' clinical, biochemical and radiological characteristics were collected, a genetic study performed and their clinical course assessed after the administration of medical treatment.

A total of nine patients (four males) took part, with a mean age of 15.3 years [11–20] and with mean

Table 1 Clinical, biochemical and radiological characteristics of the sample.

Case	Age at diagnosis (years)	Gender	Symptoms	PRL (ng/mL)	Lesion size (mm)	Visual disturbance	Involvement of other axes
1	11	F	Secondary amenorrhoea	406	9 × 11	Yes	No
2	12	M	Short stature	875	14 × 11	No	No
3	13	F	Short stature	2,673	20 × 24	No	Gonadotropic, thyroid
4	16	F	Secondary amenorrhoea	253.1	10 × 9	No	No
5	17	F	Secondary amenorrhoea	241.3	14 × 13	No	No
6	15	M	Short stature	2,049	22 × 26	No	Gonadotropic
7	20	M	Visual disturbance	3,892	38 × 25	Yes	Gonadotropic
8	17	M	Delayed puberty	456.9	12 × 10	No	Gonadotropic, thyroid
9	17	F	Primary amenorrhoea	106.6	10 × 7	No	No

F, female; M, male; PRL, prolactin level.

resting prolactin levels at diagnosis of 1,205.2 ng/mL [106.6—3,892]. Mean blood prolactin levels in male patients was 1,818.2 ng/mL, while in female patients, it was 714.8 ng/mL. MRI revealed a pituitary macroadenoma in all cases, with a mean greatest diameter of 17.6 mm [22.5 in males and 13.8 in females]. Four patients (three male) had gonadotropic axis involvement at diagnosis. Two of these also manifested secondary hypothyroidism, requiring hormone replacement therapy.

Its clinical presentation was as follows: secondary amenorrhoea in three females, primary amenorrhoea in one female, short stature in three patients (two males), visual disturbance (inferior hemianopia with central involvement in the left eye) in one male patient, and delayed puberty in another (Table 1).

Physical examination revealed delayed development of secondary sexual characteristics, all of which were in males.

Genetic testing was performed on seven of the subjects using a next-generation sequencing (NGS) panel (Ampliseq custom panel/Ion Torrent™ PGM) of the flanking exonic and intronic regions and 5'UTR regions of nine genes related to pituitary adenomas: MEN1, PRKAR1A, AIP, CDKN1B, GNAS, SDHB, SDHC, SDHD and DICER1. No pathogenic variants were found in five patients. In the other two, a variant of uncertain significance was found: c.34 G > A; p.Gly12Ser in heterozygosis in exon 1 of the SDHD gene. Genetic testing of the parents and sister of one of the patients was performed, finding that the mother also had the same variant.[3,4] In the other case, no genetic testing of family members was performed. No screening for other tumours was performed at diagnosis.

All patients were treated with cabergoline at a mean weekly dose of 1.44 mg [0.5—3 mg/week], achieving normal prolactin levels in six subjects. Prolactin levels partially decreased in the other three patients, so their cabergoline dose was progressively adjusted.

In terms of clinical response, all secondary and primary amenorrhoea cases were resolved a few months after starting treatment. At the time of writing, the menstrual cycle of all affected patients is regular. As for patients with short stature, one reached their target height after 4 years, while an adequate growth rate was observed in another after two years of treatment with cabergoline. In the case of the third patient, it is too soon to assess response, as treatment was only initiated six months ago at the time of writing. In the patient with visual disturbance, the normal field of vision was observed in the last eye examination performed three months after treatment was started.

Regarding radiological progression, MRI performed at least 6 months after the start of treatment revealed a progressive decrease in sellar mass in 6 patients. In the rest, diagnosis is recent and no imaging tests have yet been performed.

The finding of the same variant of uncertain significance of the SDHD gene in two patients (c.34 G > A; p.Gly12Ser) is striking. Although this variant has been identified in 1% of the chromosomes of cancer patients (pheochromocytoma, paraganglioma), it has also been identified in 1.1% of European–American control chromosomes (in some homozygous individuals) at a frequency of 0.007268, which is approximately 4,652 times the maximum expected allele frequency of a pathogenic variant of SDHD (0.0000016), suggesting that this variant is probably a benign polymorphism. However, since there is insufficient evidence in this regard, these patients should be closely followed up.[5–7] In summary, a similar prevalence of prolactinomas in both males and females of paediatric age was found. Prolactinomas should be clinically suspected in any paediatric patient with short stature and/or delayed puberty, and in girls with abnormal menstrual cycles. It seems important to conduct genetic testing in all young patients with pituitary adenomas, in order to identify the risk of developing other tumours and tailor specific follow-up.

Funding

This study did not receive funding of any kind.

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https://doi.org/10.1016/j.endien.2022.11.028

IGSF1 mutation as a cause of isolated central hypothyroidism

Mutación de IGFS1 como causa de hipotiroidismo central aislado

Hypothyroidism is a prevalent condition characterised by a deficiency in thyroid hormone production. Nearly all cases are of primary origin, meaning that they arise from thyroid gland abnormalities.

Central hypothyroidism has an incidence of one case per 16,000–30,000 population. It consists of a thyroid hormone deficiency as a result of dysfunction in the hypothalamus, pituitary gland or hypothalamic–hypophyseal portal circulation. It presents with decreased thyrotropin-releasing hormone (TRH), decreased thyroid-stimulating hormone (TSH) or both. TSH may be inappropriately decreased, normal for thyroxine levels or even mildly elevated since forms of TSH with limited biological activity are synthesised in some cases.[1]

Central hypothyroidism is most often seen in the context of panhypopituitarism. Isolated central hypothyroidism is a very uncommon condition, with an estimated prevalence of one out of every 65,000 people. Its primary causes are genetic and, therefore, congenital mutations. In the first report, it affected TSH subunit beta (TSHB). In subsequent reports, it affected others such as those of TRH receptor, immunoglobulin superfamily member 1 (IGSF1), transducin beta-like 1X (TBL1X) and insulin receptor substrate 4 (IRS4).[1,2] Out of them all, the most common is IGSF1 deficiency. It was first reported in 2012 and has recently been seen to account for up to 38% of cases of isolated central hypothyroidism.[3] It has an estimated incidence of one case per 100,000 population per year.[2]

We report the case of an 18-year-old male referred to endocrinology for hypothyroidism. He reported signs and symptoms of progressive asthenia and cold intolerance. His family history included autoimmune thyroiditis in his mother and maternal grandfather with isolated central hypothyroidism and primary hyperparathyroidism. Laboratory results included free thyroxine (T4) 0.48 mcg/dl (0.54–1.4) and TSH 1.11 mcIU/mL (0.38–5.3). A thyroid ultrasound yielded no findings of note, and the patient tested negative for peroxidase antibodies. All other baseline pituitary hormone levels were normal. The patient's condition was labelled isolated central hypothyroidism and replacement therapy with levothyroxine was started. Magnetic resonance imaging (MRI) of the pituitary gland revealed that the patient, like his grandfather, had a partially empty sella turcica.

When we reviewed his medical record, we saw that he had been followed up in paediatrics due to short stature, with a diagnosis of constitutional delay in growth and puberty at age 14, though with a testicular volume at the upper limit of normal (25 ml).

Taking into account the tendency towards macroorchidism and the maternal grandfather's history of isolated central hypothyroidism, IGSF1 deficiency was suspected. Specific genetic testing was performed using next-generation sequencing (NGS) of the entire coding region and the intronic flanking regions of the IGSF1, FOXE1, NKX2-5, PAX8 and TSHR genes associated with hypothyroidism. This testing was positive for IGSF1 mutation (NM_001170961.1:c.2431_2432del p.(Met811Glufs*). Given these findings, the doctor responsible for the outpatient follow-up of the grandfather was notified; whether he agreed to undergo genetic testing is unknown.

IGSF1 deficiency has X-linked inheritance and is mainly associated with congenital isolated central hypothyroidism of variable severity (variable TSH, low free T4 and low free T3) and macroorchidism. A disharmonious puberty may also accompany it with a regular increase in testicular size but a delayed increase in pubertal luteinising hormone (LH) and follicle-stimulating hormone (FSH), as well as a secondary, delayed increase in testosterone, resulting in a later pubertal growth spurt.