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Pituitary incidentalomas in paediatric age are different from those described in adulthood

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Abstract

Purpose Guidelines on pituitary incidentalomas evaluation and management are limited to adults since there are no data on this matter in the paediatric population. We aim to analyse the morphologic characteristics, hormonal profile and follow-up of these lesions in children.

Methods We have searched for pituitary incidentalomas in the neuroimaging reports and electronic medical records of the Paediatric Endocrinology Clinic of our centre. Patients with 18 years-old or less were included.

Results Forty-one incidentalomas were identified, 25 of them (62.4%) in females. The mean age at diagnosis was 12.0 ± 4.96 years-old. Headaches were the main reason that led to image acquisition (51.2%) and MRI was the imaging method that detected the majority of the incidentalomas (70.7%). The most prevalent lesion was pituitary hypertrophy (29.3%), which was mainly diagnosed in female adolescents (91.7%), followed by arachnoid cysts (17.1%), pituitary adenomas (14.6%) and Rathke's cleft cysts (12.2%). Most patients (90.2%) did not present clinical or laboratorial findings of hypopituitarism or hormonal hypersecretion. Four patients presented endocrine dysfunction: three had growth hormone deficiency and one had a central precocious puberty. Twenty-three patients (56.1%) underwent imagiological revaluation during a median follow-up time of 24.6 months (interquartile range 5.07). None of them presented dimensional progression.

Conclusions To the best of our knowledge, this is the first series of pituitary incidentalomas in pediatric age. Comparing our series with those conducted in adults, we have observed a higher preponderance of pituitary hypertrophy over adenomas, a lower prevalence of hormonal hyper/hyposecretion and lower risk of dimensional progression during follow-up.

Keywords Pituitary gland · Incidentaloma · Pediatrics · Neuroimaging

Introduction

Pituitary incidentalomas are previously unsuspected pituitary lesions that are discovered in imaging studies performed for unrelated reasons. This concept excludes lesions that were detected in exams that were carried out due to compressive symptoms or to potential manifestations of hormonal hypersecretion or hypopituitarism [1]. Incidentalomas are becoming increasingly frequent considering the increasing demand for imaging studies in clinical practice and the improvements in their technical resolution [2]. Autopsy series identified a wide variation in the prevalence of these lesions (from 1.5 to 27%) [3]. Several studies in the adulthood showed that pituitary adenomas are usually the most prevalent lesions. Rathke's cleft cysts, arachnoid cysts and pituitary hypertrophy have also been reported as rarer findings [4–6].

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Endocrine Society guidelines highlight that patients with pituitary incidentalomas should undergo clinical and laboratorial evaluation for evidence of hormonal hypersecretion and hypopituitarism. They also recommend differential analytic and imaging surveillance strategies when managing a patient with a micro or a macroincidentaloma that do not meet criteria for surgical removal [1]. However, Endocrine Society states that these recommendations are limited to adults because data on this matter are not available in the paediatric population. Several case reports throughout the literature have unveiled specific settings where the management of pituitary incidentalomas in children was particularly challenging, raising awareness about the need of a proper evaluation of these patients [7, 8].

There are few publications on paediatric sellar and suprasellar lesions. They represent a diverse group of tumours, with craniopharyngiomas comprising the vast majority of them, followed by chiasmatic/hypothalamic gliomas [9–11]. However, craniopharyngiomas and gliomas do not usually present themselves as an incidental finding. Instead, they are usually diagnosed during the investigation of headaches or visual symptoms [12]. As so, we hypothesize that the epidemiological and diagnostic features of incidentalomas in children do not match with the aforementioned ones and that they require specific management and surveillance.

The objective of this study is to analyse the morphological characteristics and hormonal profile of pituitary incidentalomas in paediatric age. Additionally, we aim to assess the management and follow-up of these patients.

Methods

This is a retrospective observational study conducted in a tertiary referral hospital. We have searched the terms "hypophysis", "pituitary", "incidentaloma" and "sella turcica" in all imaging studies reports that were performed at the Neuroradiology Department from September/2008 to September/2018. A total of 15,980 neuroradiological imaging studies were analysed. Additionally, we have reviewed the diagnosis of the patients referred to the Paediatric Endocrinology Clinic of our centre from September/2012 to September/2018. Only patients with 18 years-old or less were included.

We have considered as pituitary incidentalomas those imagiological findings that were in accordance with the definition of the Endocrine Society Guidelines [1]. All images were reviewed by two neuroradiologists that discussed the non-consensual findings. Pituitary hypertrophy of puberty was defined as a gland height greater than 6 mm and less than 11 mm in girls and 9 mm in boys, with homogeneous signal intensity in all imaging sequences, both prior and after contrast administration [13, 14]. We have excluded patients with unclear lesions in the imaging studies and those in whom the reason to request the exam was not stated in medical records.

Demographic, clinical and physical examination data were collected from electronic medical records. Patients that were evaluated by the Paediatric Endocrinology Unit due to pituitary incidentalomas in our centre usually undergo the following hormonal measurements: prolactin; ACTH and morning cortisol; TSH and free T4 levels; IGF-1 and IGFBP-3; and LH, FSH, SHBG and total testosterone/oestradiol (depending on their sex and pubertal stage). When incidentalomas involved the neurohypophysis, serum sodium and serum/urinary osmolarities were also requested. Additional basal and dynamic tests were performed upon a specific clinical suspicion or when previous laboratorial findings needed to be confirmed.

Categorical variables were expressed as frequencies and percentages and were compared using Chi square test. Continuous variables were presented as means and standard deviations, or medians and interquartile range (IQR) for variables with skewed distributions. Normal distribution was evaluated using Shapiro–Wilk test or skewness and kurtosis. Reported p values are two-tailed, and $p < 0.05$ was considered significant. Analyses were performed using SPSS Statistics 25®.

Results

We have detected 41 pituitary incidentalomas, accounting for an incidence rate of 257/100,000 patients-year. Twenty-six patients were females (63.4%) and 15 were males (36.6%), with a mean age at diagnosis of 12.0 ± 4.96 years-old. Most lesions were detected by magnetic resonance imaging (MRI) (70.7%) and the remaining by computed tomography scan (CT). The reasons that led to the imaging study acquisition are described in Table 1, with headache being the most frequent one (51.2%). Twenty-six patients (63.4%) were referred to the Paediatric Endocrinology Unit of our hospital following the incidentaloma diagnosis.

Table 1 Reasons which led to the requisition of MRI or CT scan

	n (%)
Headache	21 (51.2%)
Neurological signs	7 (17.1%)
Neuropsychomotor developmental disorders	4 (9.8%)
Ocular and visual symptoms not related with the tumour	3 (7.3%)
Cranial dysmorphia	3 (7.3%)
Other reasons	3 (7.3%)

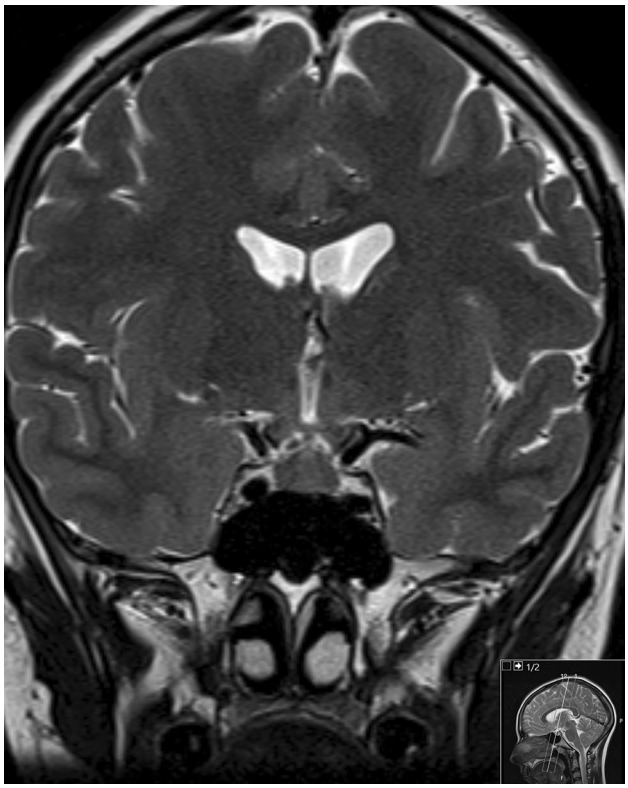

Fig. 1 Pituitary hypertrophy in a 13-year-old girl. Coronal T2 weighted MRI showing a homogeneously enlarged pituitary gland with an upward convexity

Table 2 Diagnosis of the pituitary incidentaloma

	n (%)
Pituitary hypertrophy	12 (29.3%)
Arachnoid cyst	7 (17.1%)
Adenoma	6 (14.6%)
Rathke's cleft cyst	5 (12.2%)
Neurohypophysis abnormalities	3 (7.3%)
Thickened pituitary stalk	3 (7.3%)
Pituitary hypoplasia	1 (2.4%)
Pituitary apoplexy	1 (2.4%)
Hamartoma	1 (2.4%)
Craniopharyngioma	1 (2.4%)
Undetermined cystic lesion	1 (2.4%)

Pituitary hypertrophy (Fig. 1) was the most prevalent incidentaloma, accounting for 29.3% of the cases (Table 2). Among the 12 patients with this diagnosis, 11 were females (91.7%), all of them with ages comprised between 12 and 18 years-old. In what concerns the second most frequent incidentaloma, arachnoid cysts, a male preponderance was found (71.4%). Pituitary adenomas were mostly microadenomas (< 1 cm) (83.3%) and they were diagnosed in 4 females and 2 males. Four patients had imagiological signs of hemorrhage.

Twenty-three patients (56.1%) underwent imagiological were revaluation, all of them through MRI. Patients that were referred to the Paediatric Endocrinology Unit had a greater chance of undergoing a second imaging exam to clarify the incidentaloma aetiology or to assess dimensional progression (OR 4.98; $p < 0.05$). During follow-up [median time of imagiological surveillance of 24.6 months (IQR 5.07)], most lesions remained stable (95.7%) and one (4.3%) presented dimensional reduction. No cases of lesion growth were reported.

Regarding hormonal profile, 11 patients had no record of pituitary function assessment and 2 had only been evaluated for thyroid function. A hormonal panel with the evaluation of all pituitary axis was requested in 18 patients (43.9%) and this was significantly associated with their referral to the Paediatric Endocrinology Unit (OR 18.5; $p < 0.001$). Thyroid axis was the most frequently evaluated (73.2%), followed by the gonadotropic (61.0%), adrenocorticotropic (58.5%), and growth hormone (58.5%) axis. Prolactin was the parameter less regularly assessed (41.5%). Most patients (90.2%) did not present clinical or laboratorial findings suggesting hypopituitarism or hormonal hypersecretion. After the detection of the pituitary incidentaloma (namely a pituitary-hypothalamic hamartoma and an ectopic neurohypophysis), two patients were diagnosed with growth hormone (GH) deficiency and are currently being treated with somatropin. One patient with pituitary hypoplasia is currently being investigated for GH deficiency after two consecutive blood analysis revealing low IGF-1 values (IGF-1 z-score of -1.4 and -2.4). Central precocious puberty (CPP) was diagnosed in a male with a microadenoma and he was treated with GnRH agonist (triptorelin). The patient that presented a craniopharyngioma had no pre-operative hormonal deficits, but ophthalmological evaluation revealed a mild visual field defect due to optic chiasm abutting and he underwent surgery. He is currently being followed in the Paediatric Endocrinology Unit due to post-surgical pan-hypopituitarism, and undergoing hormonal replacement with desmopressin, hydrocortisone, levothyroxine and somatropin. None of the remaining incidentalomas was surgically managed.

Discussion

In this study, we report three main findings. First, pituitary hypertrophy is the most prevalent incidentaloma in paediatric age and it occurs mostly in female adolescents. Secondly, most lesions are not associated with hormonal hypersecretion or hypopituitarism, but careful clinical and laboratorial evaluation allowed early diagnosis and treatment of those with endocrine abnormalities. Third, none of the

incidentalomas in our study showed a significant dimensional progression during the follow-up period.

Data on pituitary incidentalomas in paediatric age are lacking. Therefore, we have discussed our findings by comparing them with those of large adult series. Headaches were the main reason that led to image acquisition in our patients like previously stated in adults [4, 5, 15–17]. The association between headaches and sellar masses remains controversial as a multifactorial link between chronic headaches and pituitary tumours has been suggested [18]. Moreover, headaches improvement has been described in some post-surgical patients [19]. These facts question if lesions detected during headache work-up should be considered as incidentalomas. However, all the publications we have cited throughout this manuscript have considered them as so and we have kept with this concept. We have found a female preponderance that is also in accordance with prior reports [4–6, 16]. This probably does not translate real biological differences in incidentaloma prevalence considering that autopsy studies do not confirm a skewed distribution by gender and the higher prevalence of headaches in female children [3, 20].

Pituitary hypertrophy was the most prevalent finding in our cohort, accounting for 30% of the incidentalomas. None of these patients presented with hormonal hypersecretion. This differs from adult series that consistently pointed out adenomas as the most frequent lesion [4–6, 15]. Pituitary hypertrophy has also been described in adult series but with lower prevalences (from 2.4 to 7.3%) [4, 5]. Previous neuroradiological studies have described an increased pituitary gland height in adolescents, mainly females, corroborating our findings. This situation has been interpreted in the context of hypothalamic-pituitary-gonadal axis activation during puberty, although its higher prevalence in girls remains puzzling [21–23]. Owing to the recognition of pituitary hypertrophy in this population as physiological, Chanson et al. suggested that after an initial laboratorial evaluation without identifiable abnormalities, hormonal and frequent neuroradiological follow-up seems to be unnecessary in this setting [24]. In what concerns arachnoid cysts, despite the limited number of cases, we found a male preponderance consistent with previous studies [25]. Most of the adenomas incidentally detected in children were infracentimetric, contrasting with the greater prevalence of macroadenomas in adults [4–6, 15–17].

None of the patients that underwent imagiological revaluation presented significant lesion growth. A meta-analysis on this matter in adulthood has found that 8.2% of incidentalomas enlarged each year, with microincidentalomas showing a smaller percentage (1.7% per year) [26]. Two studies with median surveillance times comparable to ours (between 24 and 36 months), have found dimensional progression in 12% of the incidentalomas [5, 15]. These findings guided the Endocrine Society recommendation that a MRI of the pituitary should be performed 6 months after the initial scan if the lesion is a macroincidentaloma and 1 year after the initial scan if it is a microincidentaloma [1].

The prevalence of hormonal abnormalities during the work-up of a pituitary incidentaloma in our study (9.8%) was lower than those described in adult series. Hypopituitarism has been consistently reported as more frequent (25–61%) than hormonal hypersecretion (8.8–21%) throughout the studies. Hypogonadotropic hypogonadism and prolactinomas are the most common findings in each of these categories, respectively [4, 6, 15–17]. The rarity of endocrine dysfunction in pediatric age can probably be explained by the low rate of adenomas and the preponderance of smaller lesions. GH axis was the most commonly disturbed in children being evaluated for incidentalomas. One of the patients presented a hamartoma, which has been mostly associated with CPP, but case reports have also identified GH deficiency in children with this type of lesion [27, 28]. In addition, both ectopic neurohypophysis and pituitary hypoplasia have been commonly described in patients with GH deficiency [29]. CPP was diagnosed in a boy with an incidentally found microadenoma but there is probably no causal association according to literature [30]. However, considering that not all patients were referred to the Paediatric Endocrinology Unit to undergo appropriate hormonal assessment, endocrine dysfunction maybe be underestimated in our cohort.

In conclusion, pituitary incidentalomas in children seem to have different patterns than those detected in the adulthood, highlighting that specific guidelines regarding this population are needed. To the best of our knowledge, this is the first study on pituitary incidentalomas in paediatric age. The authors consider that children with these lesions should undergo an appropriate baseline hormonal assessment. Considering the high prevalence of physiological pituitary hypertrophy in our series and that most incidentalomas neither presented hormonal hyper/hyposecretion nor dimensional progression, some children will not probably benefit of the cumbersome incidentaloma follow-up protocols established by adult guidelines. Additional long-term multicentre studies should continue to address pituitary incidentalomas in order to individualize their work-up in paediatric age and the need for surveillance throughout adulthood.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Human and animal rights All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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