

Pediatric adrenal incidentaloma

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ABSTRACT

The term of "incidentaloma" involves multiple disciplines of the medicine, especially on the era of modern medicine with massive progress of investigations tools that increased the epidemiological implications of this entity. "Endocrine incidentaloma" represents a term mostly used for adrenals and pituitary glands (and less used for thyroid where it is replaced by the term of "thyroid nodule"). Adult adrenal incidentaloma (AAI) is expected to be found up to 5-20% of population depending on age group, co-morbidities, radiological/imaging method (the incidence increases with age), and not in children. We aim to overview the spectrum of pediatric AI (PAI) as an umbrella term for various histological and endocrine conditions. This is a brief narrative review of literature. Inclusion criteria are: PubMed published papers, in extenso articles (English language), the year of publication between 2016 and 2021; the selection is based on clinical relevance. A number of 70 references is included. PAI may be related to various tumors of the cortex and medulla, while AAI mostly means an adrenocortical adenoma with a very good prognostic. AAI diagnostic (based not only on radiological, but also an endocrine assessment) exceptionally underlines an adrenocortical carcinoma or evolves to a malignancy while in pediatric population the eventuality of an incidental adrenocortical carcinoma is not so rare (the non-functional pattern is more frequent in children than in adults). Neural crest-derived tumors may be located at adrenal levels; while ganglioneuroma is a benign tumor which typically respects the incidental detection, neuroblastoma is mostly aggressive and the clinical presentation suggestive for a malignancy is more frequent rather than a completely asymptomatic picture. 10-14% of pheochromocytomas are incidentally detected; however, the adrenalectomy is imperative, regardless the phenotype. PAI represents a large multidisciplinary field which is still a matter of debate in certain areas. The key message is the fact that accidental detection of an adrenal mass on an apparently healthy child needs careful examination; serial follow-up is less likely the elective approach (opposite to adult population) since adrenalectomy provides adequate histological report in order to sustain the endocrine and imaging workup.

Keywords: adrenal incidentaloma, adrenal tumor, ganglioneuroma, pheochromocytoma, adrenocortical carcinoma, puberty, adrenal mass, metastasis

INTRODUCTION

The term of "incidentaloma" involves multiple disciplines of the medicine, especially on the era of modern medicine with massive progress of investigations tools that increased the epidemiological implications of this entity (1,2). The finding of an incidentaloma as an accidental event (as shown by the

name itself) is highly feasible with advanced imaging techniques, but its detection might also be done during a surgical or an endoscopic procedure which is performed for an apparently unrelated condition etc. (3,4).

"Endocrine incidentalomas" as term mostly used for adrenals and pituitary glands (and less used for

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thyroid incidentaloma since the term of “thyroid nodule” replaced it in majority of situations) also includes, a part from incidental detection, a very good outcome after the tumor is evaluated (meaning negative hormonal profile and a low rate of growth, thus the indication of its removal is hardly established since it is unnecessary) (5,6).

However, many studies use the term of “incidentaloma” located at the level of an endocrine gland as a strictly radiological/imaging event, not necessarily associating a benign behavior, so controversies still exist (as also seen, for instance, in the management of adrenal incidentaloma according to different current guidelines) (7,8).

Also, another open issue is related to the detection of an apparently asymptomatic tumor in a subject who is evaluated (during screening or during follow-up) for prior or concurrent malignancy: this may be a metastasis or a true incidentaloma; is it adequate to call a metastasis an “incidentaloma” under these specific circumstances? (9,10).

Opposite to pituitary gland, adrenal incidentaloma is somehow expected to be found in adults, the incidence increases with age, up to 5-20% of population depending on age group, co-morbidities, radiological/imaging method etc. (2,11).

AIM

We aim to overview the spectrum of adrenal incidentaloma as an umbrella term for various histological and endocrine conditions, focusing on pediatric population, children and teenagers, opposite to adult/general population.

METHOD

This is a brief narrative review of literature. Inclusion criteria are: PubMed published papers, *in extenso* articles (English language), the year of publication between 2016 and 2021; the selection is based on clinical relevance. 70 references are included. The literature data is structured on subsections depending on underlying diagnostic.

THE UMBRELLA TERM OF “ADRENAL INCIDENTALOMA”

As mentioned above, it is an extremely rare event the admission of an asymptomatic child is for an accidental detection of a mass at the level of adrenal glands, and in majority of cases this does not mean that the tumor is an adrenocortical adenoma (with or without subclinical autonomous cortisol secretion) as we generally refer to for an adult subject (12,13). In adults, the diagnostic of an adrenal incidentaloma means a non-functioning adrenal tumor of the cortex (unilateral or even bilateral in less

than 5-10% of cases), with less than one third of cases displaying mild symptoms due to mild secretion of cortisol (as cardio-metabolic complications, bone loss etc.) (14,15). This rarely is managed by the indication of adrenalectomy, unless the tumor progresses during follow-up (which is mostly unlikely) or at least one diameter reaches the cutoff of 4 centimeters (cm) or clinical complications are considered to be strongly associated with positive endocrine secretion (even subclinical) (16,17).

In most adult cases of adrenal incidentalomas, adrenal surgery is unnecessary, the serial evaluation representing the key approach (17,18). The imaging follow-up is more frequent within the first 2-3 years since initial diagnostic (for instance, every 6 months), and less frequent as time goes by since first identification (18,19). But in pediatric subjects this scenario is less likely; for example, if initial negative endocrine balance was confirmed in addition with non-suspected features for a malignancy at imaging assays, a more consistent follow-up is essentially required and, eventually, the tumor removal is useful to provide an adequate histological report (and, of course, immunohistochemistry report) (20,21). The decision is based on a multidisciplinary panel of evaluators, including pediatrician, endocrinologist, radiologist, oncologist, surgeon etc. (22). The adrenal lesion may be hormonally active or not, the young patient might be already known with a genetic syndrome with endocrine implications, while the tumor aspect at abdominal ultrasound, computed tomography or magnetic resonance imaging might be heterogeneous, with either cystic, solid or mixt appearance, involving a single or both glands (23,24).

ADRENOCORTICAL CARCINOMA

Opposite to adult population where an initial diagnostic of adrenal incidentaloma (after performing a radiological and endocrine assessment) rarely underlines an adrenocortical carcinoma or evolves to a malignancy of the adrenal cortex, in pediatric population the eventuality of an adrenocortical carcinoma is not so rare (25,26). The need of practical biomarkers under these conditions is imperative since the adrenal cortex malignancy has a very poor outcome and early detection might help (26-28). A retrospective study from Mayo Clinic included non-neuroblastic tumors which were resected between 1988 and 2018 (a paper published in 2020 by Traynor et al.) (29) Among 50 adrenalectomies, 15% were initially admitted for an adrenal incidentaloma (29). 20% of the tumors were adrenocortical carcinoma (29). The pitfalls of adrenocortical carcinoma diagnostic in children is the non-functional pattern which is more frequent in children than in

adults (where 70-90% of cases are hormonally active) (30,31). In cases with cortisol and androgen abnormal secretion (causing Cushing syndrome, precocious puberty, virilization syndrome and reduced velocity of growth, *etc.*) the scenario of adrenal incidentaloma is dismissed (32,33).

GANGLIONEUROMA/NEUROBLASTOMA

Neural crest-derived tumors may be located at adrenal levels; while ganglioneuroma is a benign tumor which typically respects the incidental detection, neuroblastoma is mostly aggressive; its clinical presentation is typically suggestive for a malignancy rather than a completely asymptomatic picture (34,35). Ganglioneuroma might seem like a harmless mass, but until histological confirmation, there is no such tumor in pediatric population (opposite with the good prognostic of adrenal incidentalomas in adults where adrenalectomy is rarely needed) (36,37).

PHEOCHROMOCYTOMA

Pheochromocytomas (and paragangliomas) represent a part of the vast family named neuroendocrine neoplasia which also includes hormonally active tumors like glucagonoma, somatostatinomas as well as gastro-entero-pancreatic neuroendocrine tumors (38,39). The tumor, originating from chromaffin cells of the adrenal medulla, is found in 10% as an adrenal incidentaloma based only on radiological definition, not on radiological + endocrine consensus (40,41). 2-4% of children with high blood pressure may have the tumor, but the active investigations in order to rule out a secondary cause of arterial hypertension does not represent the scenario of an adrenal incidentaloma (42). A study published by Virgone et al. in 2020 showed among 1000 patients who were registered with rare pediatric tumors, diagnosed between 2000 and 2019, 50 cases with pheochromocytomas and paragangliomas (43). In this study, 7 (out of 50) persons had the diagnosis established as an adrenal incidentaloma (43). Regardless incidental detection, a pheochromocytoma requires immediate surgery (with perioperative alpha and beta-blockage of adrenergic receptors), as well as genetic workup (44-46).

GENETIC SYNDROMES

Adrenal tumors in patients with genetic syndromes or different gene mutations represent a large domain (47,48). In cases with already known

genetic anomalies, the identification of an adrenal tumor does not respect the “incidental” pattern of detection since it is expected to be found in relationship with the genetic configuration and a certain patient’s age (49,50). Rarely, starting from an adrenal incidentaloma diagnostic, a previously unknown genetic condition is detected (51-53). We mention pheochromocytoma in multiple endocrine neoplasia type IIA (in addition to medullary thyroid cancer and primary hyperparathyroidism) or, extremely rare, type 1 neurofibromatosis (54,55). TP53 mutation causes isolated adrenocortical carcinoma, or syndromic phenotype as Li-Fraumeni syndrome or Li-Fraumeni-like syndrome (56,57). Beckwith-Wiedemann syndrome may be sometimes be associated with an adrenal tumor (58-60). Adrenocortical adenoma or carcinoma has been reported, and also neuroblastoma (61-63). Neuroblastoma may display a cystic component, mimicking a classic adrenal cyst (64-66). Early presentation within the first weeks of life needs antenatal diagnostic which is essential for prognostic (64-66). Also, Carney complex may associate Cushing syndrome of adrenal cause, thus the pattern of adrenal tumor displayed as incidentaloma is less likely during years of childhood (67-70).

DISCUSSIONS

Considering the large field of pediatric adrenal incidentaloma, the most important subjects that are currently opened to controversies and intensive pros and cons debates or incompletely understood until now days are the following: non-aggressive markers of malignant behavior in a newly detected tumor of the adrenal gland; clear criteria of defining an adrenal incidentaloma and whether it is truly appropriate to use the term in pediatric population knowing various underlying histological types; protocols of hormonal, genetic and imaging workup in syndromic cases confronting adrenal tumors (others than multiple endocrine neoplasia syndrome).

CONCLUSIONS

Pediatric adrenal incidentaloma represents a large multidisciplinary field which is still a matter of debate in certain areas. The key message is the fact that accidental detection of an adrenal mass on an asymptomatic child needs careful examination; serial follow-up is less likely the elective approach (opposite to adult population) since adrenalectomy provides adequate histological report in order to sustain the endocrine and imaging workup.

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