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CYSTIC ADRENAL LESIONS: FOCUS ON PEDIATRIC POPULATION (A REVIEW)

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Abstract

Background and aim*. The cysts may potentially affect any organ; adrenals cysts are rare. This is a review of the literature regarding adrenal cysts, focusing on children and young adults.*

General data. *Three major types have been described: pure cysts (endothelial, epithelial, and hemorrhagic or pseudocyst), parasitic (as hydatid) cysts and cystic part of a tumour (most frequent are neuroblastoma, ganglioneuroma, pheocromocytoma, and teratoma). The complications are: bleeding, local pressure effects; infection; rupture (including post-traumatic); arterial hypertension due to renal vessels compression. Adrenal hemorrhage represents a particular condition associating precipitating factors such as: coagulation defects as Factor IX or X deficiency, von Willebrand disease, thrombocytopenia; antiphospholipid syndrome; previous therapy with clopidogrel or corticosteroids; the rupture of a prior tumour. At birth, the most suggestive features are abdominal palpable mass, anemia, and persistent jaundice. Adrenal insufficiency may be found especially in premature delivery. The hemorrhage is mostly self-limiting. Antenatal ultrasound diagnosis of a cyst does not always predict the exact pathology result. The most important differential diagnosis of adrenal hemorrhage/hemorrhagic cyst is cystic neuroblastoma which is highly suggestive in the presence of distant metastases and abnormal catecholamine profile. The major clue to differentiate the two conditions is the fact that the tumor is stable or increases over time while the adrenal hemorrhage is expected to remit within one to two weeks.*

Conclusion. *Pediatric adrenal cysts vary from simple cysts with a benign behavior to neoplasia- related lesions displaying severe prognosis as seen in cystic neuroblastoma. A multidisciplinary team is required for their management which is conservative as close follow-up or it makes necessary different surgical procedures in cases with large masses or if a malignancy suspicion is presented. Recently, laparoscopic approach is regarded as a safe procedure by some authors but generally, open surgery is more frequent used compare to adults; in most cases the preservation of normal gland is advisable.*

Keywords: adrenal cyst, adrenal hemorrhage, cystic neuroblastoma

Introduction

Adrenal lesions, either containing solid or liquid material, comprise a wide area of conditions which may be diagnosed during fetal life up to advanced ages [1,2,3]. Tumors of the adrenal cortex have a predominant endocrine behavior while the underlying pathological report typically involves adenoma, rarely nodular hyperplasia (often bilaterally), and exceptionally a carcinoma [4,5,6,7]. The adrenal medulla is the origin of tumors such as pheocromocytoma, ganglioneuroma, ganglioneuroblastoma [8,9,10]. The glands may be a

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secondary site of a prior cancer spreading, regardless unilateral or bilateral pattern [11,12,13]. The most frequent neoplasia with adrenal involvement is breast or lung cancer, and lymphomas [14,15,16]. Other rare adrenal lesions especially with tumor appearance are myelolipoma, neurofibroma, hamartoma, xanthomatosis, amyloidosis, granulomatosis [17,18,19]. The adrenal bed may locate masses of non-adrenal origin, like those arising from the pancreas, spleen or kidney and rarely imagery artefacts need to be differentiated [20,21,22]. Knowing this large panel of potential diagnosis related to an adrenal lesion, the cysts of this gland are rare conditions which may be recognized at any age, following the scenario of an incidentaloma or severe general disturbances [23,24]. A cystic incidentaloma does not necessarily associate a more severe prognosis since the term is currently accepted in endocrinology for pituitary and adrenal glands accidentally discovered tumors mostly with non-secretor profile and minimum risk of increasing the dimensions [25,26].

Objective

Our aim was to review the literature regarding the cystic lesions of the adrenal glands especially in children and young adults, based on a PubMed database guided research. The data are grouped based on the idea that an adrenal cyst may accidentally discovered during a routine abdominal ultrasound and the underlying diagnosis involves the general practitioners, pediatricians, endocrinologists, internists, surgeons, etc.

General data

The concept of cyst

The term of "cyst" is used in pathological conditions and it represents a closed structure surrounded by a capsule (a sac-like mass), either isolated or multiple-sited [27,28]. Anatomically, a cyst is a sac containing either liquid, gaseous or semi-solid substances, potentially involving any organ and varying in size from microscopic to extremely large (up to the level of displacing the host or neighboring organs) [29,30].

Abdominal cyst & differential diagnosis

While most cysts are benign, some may be tumors and be formed inside of tumors (these have a higher malignancy potential), so their pathogenic environment is related to a solid tumor, genetic anomalies (with or without a solid tumor association), infections (including parasites), embryo-fetal defects, blockage of an otherwise normal duct (with secondary fluid collection) and trauma (impact injury that breaks a vessel) [31,32,33].

The abdominal cysts we mention especially related to pediatric population may be located at the liver, for instance hepatic hydatid cyst, mesenchymal hamartoma, traumatic cystic lesions [34,35,36]. Biliary ducts cysts such as choledochal cysts are rare, while the mesentery area sometimes involves lymphatic malformation, pure mesenteric cysts or traumatic pseudocysts [37,38,39,40,41]. Solid organs such as spleen may associate simple cysts or vascular malformations; pancreatic cysts aspects are mostly related to pseudocysts or cystadenoma [42,43,44]. Kidneys display cyst-like lesions such as cystic Wilms tumors or multicystic dysplastic kidney, etc. [45,46,47]. Simple renal cysts have also been described in pediatric population at routine computed tomography scans, for example 69 cases were diagnosed after 2991 scans in one study between 2007 and 2009 [48].

This complex picture of abdominal cystic lesions is fulfilled by adrenal cysts which are recognized in pediatric as well as adult population. The first lesion having this site was described in 1670 and subsequently more cases were published together as a series of seven by Henschen in 1906; and by Reimann and Guyton who published some observations in 1947 related to four papers that were found during a 10-year period in the American literature [49,50]. Their work as well as the data provided by Stock on the same year currently represents the first studies available on PubMed on this matter, followed by the 1950 article by Moore and Cermak regarding a fatal outcome in a child with both adrenal cysts and insufficiency [51,52]. An early series of cases (on 83 reports) and classification is from 1956 based on the data of Blumenthal and Probstein [53].

Types of adrenal cysts

Cystic lesions of the adrenals, although exceptionally rare, may be grouped in three main types: "pure" cystic types, parasitic cysts and cystic part of an otherwise solid tumor usually related to a process of necrosis or hemorrhage [54,55].

Classical (or "pure") type of cysts includes three different sub-types. The most frequent is vascular or endothelial cyst which has either lymphangiomatous or hemangiomatous origin [56]. Adrenal lymphangiomas have a benign behavior; a review published in 2015 found 53 cases reported in literature (including adults): females were more affected and one third had no symptoms before surgery [57]. Adrenal hemangiomas also have a good prognosis (that is why it is possible to be diagnosed during adult life) but surgical removal is considered in most situations with high diameters and in those where a hemorrhagic cyst is suspected with further potential of development [58].

Coming second as prevalence is the hemorrhagic cyst, also called pseudocyst or hemorrhagic pseudocyst [59]. (Figure 1+2) Hemorrhagic cyst in children is associated with: pre / peri-natal stress; hypoxia; septicemia; hypotension; dehydration [60,61]. The vascular etiology is not accepted by all the authors (and an abdominal trauma may be enough to cause the lesion in some cases) thus the hormonal profile needs to be checked in all cases [62]. This type of cyst has walls of fibrous tissue; it characterized by the lack of epithelial & endothelial lining; and it is mostly the result of a prior hemorrhage [63]. The lesion is similar

with other prenatally developed cysts as seen in lung, spleen, and the increased potential of regression has been found to be correlated with homogenous aspects opposite to multi- lobulated structures [64].

Adrenal hemorrhagic cyst associated with a local small blood vessel anomaly on a pre-pubertal boy without birth trauma or genetic/general conditions

The rarest sub-group is the epithelial cyst, named true cyst which is related to a congenital glandular sac and associated liquid retention [65]. **(Figure 3)**

The adrenals are not a typical site for parasites, yet hydatid cyst formed by the larva of a parasite has been described [66,67].

The tumors of the adrenals described most frequently with a cystic component in children and young adults are: neuroblastoma, ganglioneuroma, pheocromocytoma, teratoma, and, exceptionally, adrenocortical carcinoma/ adenoma [68,69,70]

Pheochromocytoma may suffer necrosis and the tumor become semicystic or semisolid [71]. The cystic aspect has been found in bilaterally, familial, genetic conditions as von Hippel-Lindau disease including hemangioblastomas, pancreatic cysts, renal cancer (autosomal dominant inheritance) [72]. In pediatric population, the adrenal tumor may be the only or the first manifestation of the syndrome [73].

The cystic (mature) adrenal teratoma represents a rare germ cell neoplasia with an atypical site at the level of the gland; usually the first recognition is based on imaging findings not on symptoms, and more frequently the diagnosis is established in children than adults, including a prenatal identification of an adrenal lesion, which might improve the outcome since an early diagnosis and total resection with histological confirmation is essential [74,75].

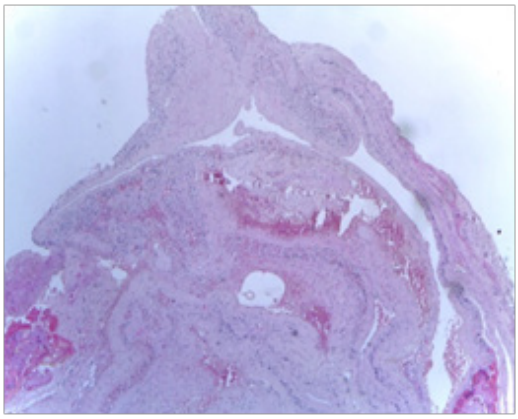

Figure 1A. 40X magnification.

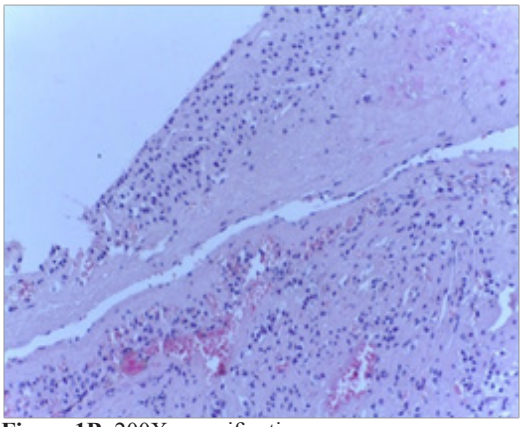

Figure 1B. 200X magnification.

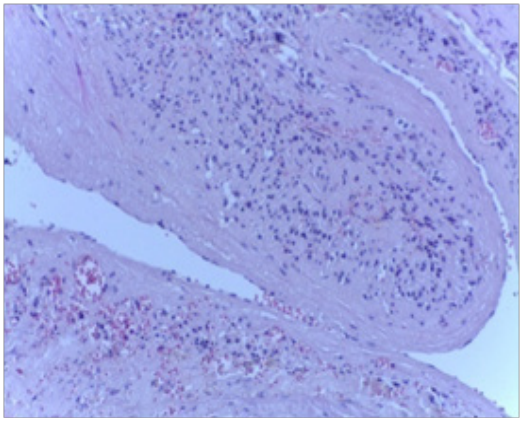

Figure 1B. 400X magnification.

Figure 1. Pathological exam: hematoxylin eosin stain.

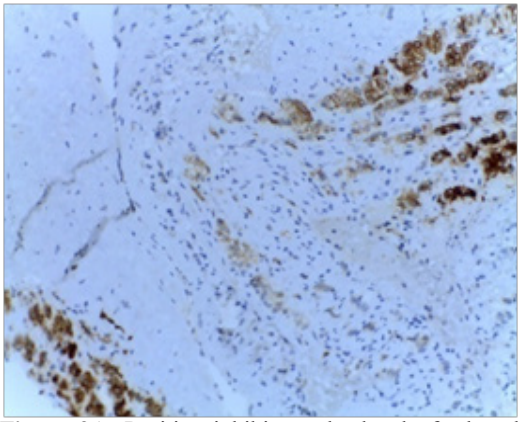

Figure 2A. Positive inhibin at the level of adrenal cortex (200X).

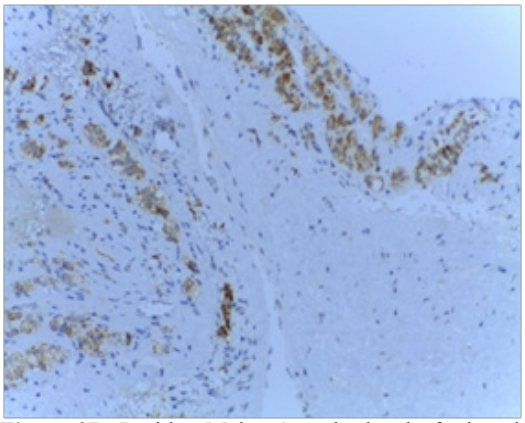

Figure 2B. Positive Melan A at the level of adrenal cortex (200X).

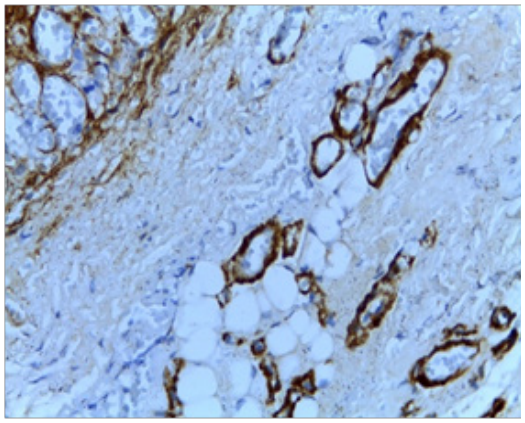

Figure 2C. Positive Actin at the level of blood vessels and stromal area (200X).

Figure 2. Immunohistochemistry examination.

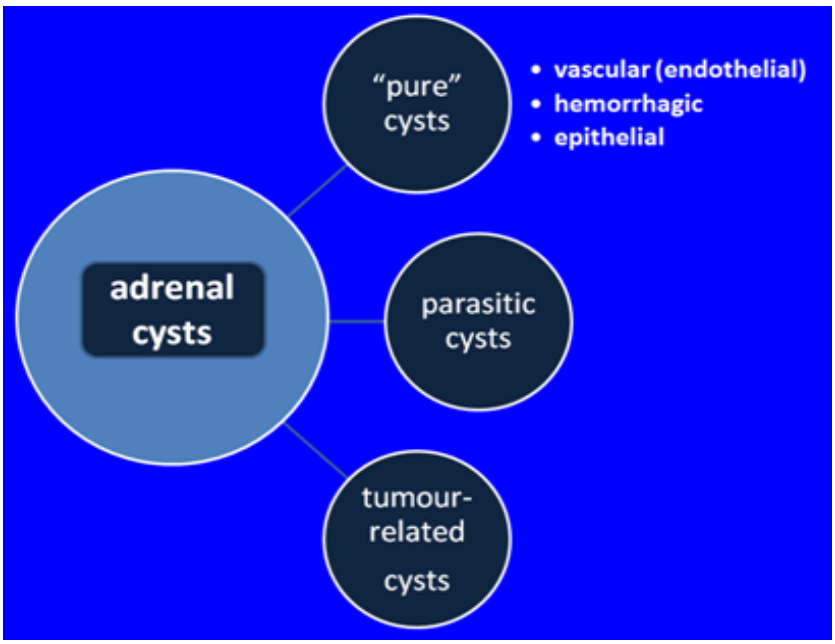

Figure 3. Main types of cysts involving the adrenal glands.

Evaluation of Adrenal Cysts

The evaluation of a cystic lesion includes imaging scans such as ultrasound, computed tomography or magnetic resonance. Biopsy is not recommended in most of cases. A complete endocrine panel is necessary for the adrenal profile.

Cysts complications

Generally, the cyst early discovery and good prognosis is related to the tumor/lesion size; patients' age and pubertal development; the presence of abdominal pain, the palpable mass or lump and potentially hormonal dysfunction (with or without genetic background) [76]. The complications are: bleeding into the cyst; local pressure effects; cyst infection; rupture of the cyst (including post-traumatic cyst rupture); arterial hypertension due to renal vessels compression [77,78].

Particular conditions of adrenal pediatric cysts

Adrenal hemorrhage may be spontaneous, but a number of precipitating factors have been involved such as: anticoagulation; pre-existing benign adrenal cyst; coagulation defects like Factor IX or X deficiency, von Willebrand disease, thrombocytopenia; antiphospholipid syndrome; previous therapy with clopidogrel or corticosteroids; the rupture of a prior tumor [79,80,81]. The hemorrhage is mostly self-limiting and the spontaneous resolution is the usual outcome; yet some cases have been reported in correlation with gastrointestinal diseases, therefore close surveillance in the peri-natal period is necessary [82]. A prenatal diagnosis of the adrenal hemorrhage is possible as generally it is for adrenal and thoracic cysts of non-hemorrhagic type; antenatal ultrasound does not always predict the exact pathological report but it is extremely important for further management of the newborn, and eventually for informing and counseling the future parents [83,84]. The right adrenal is more often affected than the left one, and left site may associate renal vein thrombosis (or thrombus at other levels if a prior pro-thrombotic condition is presented) [85]. The clinical neonatal findings in severe cases are abdominal palpable mass, anemia, and persistent jaundice [86,87]. Adrenal insufficiency may be found especially in premature delivery [88]. Also, the bilateral hemorrhagic event may be seen in correlation with Beckwith-Wiedemann syndrome (complete or incomplete forms) [89]. The syndrome associates macroglossia, abdominal wall defects, visceromegaly, gigantism, hemi-hypertrophy, hypoglycemia, and high risk of malignancy (including neuroblastoma), which requires close follow-up or even resection in case of a persistent cystic lesion of the adrenals [90,91].

During the neonatal period the most important differential diagnosis of adrenal hemorrhage is **cystic neuroblastoma** which is highly suggestive in the presence of distant metastases and abnormal catecholamine profile [92]. The major clue to differentiate the two conditions is the fact that the cystic tumor is stable or increases over time while the adrenal hemorrhage is expected to remit within one to two weeks [93]. The hemorrhagic structure remission has different stages: acute (while the adrenal cystic mass has variable echogenicity), sub-acute with hypoechoic ultrasound pattern due to liquefaction and later on a hyperechoic structure due to clot retraction and potential calcification is registered [94]. The cystic neuroblastoma associates an aggressive profile (including metastasis at the moment of first diagnosis) and requires a multi-disciplinary team [95]. The tumor arises from adrenal or any neural crest element; the ultrasound pattern is anechoic or complex echogenic, and half of cases have calcifications [96].

Adrenal cysts management

There is no standard management; small cysts may be followed up by ultrasound, computed tomography, magnetic resonance imaging; glucocorticoid replacement is necessary if adrenal insufficiency is caused by bilateral adrenal hemorrhage; since the pre-operatory assessment does not definitively distinguish the malignant lesions, surgery may represent on option [97,98]. In cases with lesions larger than 3 centimeters, associating endocrine disturbances, local symptoms or rapid growth, surgical removal should be taken into consideration or, alternatively, cyst un-roofing, exploratory laparotomy [99,100,101]. There is no general consensus if laparoscopy or open surgery should be recommended but, opposite to adults, the procedures with adrenal parenchyma preservation are recommended [102,103]. Minimally invasive surgery in children may be used in adrenal neuroblastoma with good results regarding the safety and effectiveness [104]. Imaging investigations allowing antenatal diagnosis of a cystic mass should be performed, followed if necessary by early surgery after birth [105]. Conservative therapy is recommended for adrenal hemorrhage but close check-up is necessary; generally a tumor identified before birth or immediately after without a precise diagnosis may be followed for one month without worsening the prognosis [106].

Conclusion

Adrenal cysts are rare lesions in the pediatric population, varying from pure cysts with a benign behavior to tumor-related types displaying severe prognosis, like those in cystic neuroblastoma. A multidisciplinary team is required for their management, which is conservative as close follow-up (including the cases with ante- or peri- natal diagnosis of an adrenal hemorrhage); or it makes necessary different surgical procedures in cases with large masses or suspected malignancy. Recently, laparoscopic approach is regarded as a safe procedure by some authors but generally, open surgery is more frequently used than in adults; in most cases the preservation of the normal gland is advisable.

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