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Review

Pediatric adrenal cortical carcinomas: Histopathological criteria and clinical trials. A systematic review

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ABSTRACT

Adrenal tumors are quite rare in infancy and childhood with the exception of neuroblastoma. In fact, adrenocortical tumors (ACT) account for only 0.2% of all malignant cancers in children and adolescents. According to a multicenter registry investigation, the median interval between first endocrine symptoms and the diagnosis of ACT is 5 months, and death is seen in 38% of patients, who suffer from tumor progression following the diagnosis in about 2½ years. The prognosis of pediatric ACC is poor with a 5-year event-free survival of 54%. To face this dreadful scenario, a few decades ago the International Pediatric Adrenocortical Tumor Registry (IPACTR) was established. Moreover, Children's Oncology Group (COG) and National Cancer Institute (NCI) have approved several clinical trials designed to investigate new treatment options in pediatric ACT. In this systematic review, we summarize the diagnostic histopathologic criteria, bio-markers, and clinical trials of this challenging diagnosis. Eleven pediatric ACT trials were reviewed in our investigation. Two out of 11 studies were conducted in Brazil showing apparently an increased rate of germline mutation-related pediatric ACT. A heterogeneous methodology was evident with four non-randomized clinical trials, three prospective cohort studies, and four retrospective case-control studies limiting higher statistical approach. Tumor histology remains the backbone to diagnose ACT creating a common investigative platform and potentially supporting studies aiming to increase international collaborative research, which is crucial for this challenging disease.

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1. Introduction

Adrenal tumors, apart from neuroblastoma, are quite rare in infancy and childhood substantiated by both universal teaching and clinical practice. In infancy and childhood, both benign and malignant tumors may be hormonally active and present clinically with excessive hormone production, which manifests in typical clinical syndromes [1]. Adrenocortical carcinoma (ACC) is the rare malignant counterpart of adrenal neoformations of childhood and adolescence, with an incidence of 1.5 per million per year [2].

Adrenocortical tumors (ACT) account for 0.2% of all malignancies in individuals younger than 20 years [3]. The clinical manifestations and biologic behavior of pediatric ACT seem to be distinct from the ACC observed in adulthood. The most common manifestation is virilization,

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which can occur alone or in combination with other adrenal hormonal imbalances [3]. According to a multicenter registry investigation (254 patients), the median interval between first endocrine symptoms and the diagnosis of ACT is 5 months, and 38% patients die due to tumor progression within 2½ years approximately [1]. There are no clinical differences between the two genders [4]. Pediatric patients with ACT seem to present more endocrine dysfunction features (virilization or feminization) and *TP53* mutations compared to adults indicating that there may be a robust association between *TP53* mutations and ACT diagnosis in the first decade of life [5]. As a fact rescountered in both textbooks and clinical practice, there is still difficulty to discriminate benign from malignant pediatric ACT based on histopathological criteria [4].

The prognosis of pediatric ACC is poor with a 5-year event-free survival of 54% [6]. Therefore, an outcry in the scientific and lay communities brought to the creation of some form of new collaboration aiming to establish a systematic interdisciplinary consortium among different countries worldwide. A few decades ago was established the International Pediatric Adrenocortical Tumor Registry (IPACTR) to create a new investigative platform [7]. IPACTR collects clinical and laboratory features, treatment practices, and outcome data for children with ACT, as well as systematically investigates how to improve patient outcomes. Other organizations such as Children's Oncology Group (COG) and National Cancer Institute (NCI) have approved several clinical trials designed to investigate new treatment in pediatric ACT [8]. In this systematic review, we will summarize the diagnostic criteria, biomarkers, clinical trials and discuss the current challenges, which seem to persist in pediatric ACT.

2. Material and methods

Histopathological criteria were revised in detail using reviews and studies identified on PubMed and Google Scholar using “histology”, “pathology”, “adrenocortical tumor”, and “review” (see below for details). This initial part should be considered a “narrative review”, while the “clinical trials' section should be considered a “systematic review”.

To summarize the clinical trials in pediatric ACTs diagnosis, chemotherapy and surgical managements, we systematically searched the published literature in several main online databases including PubMed and government clinical trials databases from US, UK, and Europe. The inclusion standard criterions for literature are: 1) Studies published in the past 30 years from 1985 to 2015; 2) Studies focused on young patients ACTs and ACCs (age below 30 years old, including infants, children, adolescents and young adults). 3) Studies published in English, only peer reviewed and empirically published.

After the duplicates were removed, 40 articles remained and considered appropriate according to our inclusion criteria. Both the pediatric ACT trials and solid tumor trials with available results were involved in our review (number = 22). After reviewing the full text and screening age range and ACTs cases enrollment, 11 additional articles were classified as ineligible for our study and 11 peer-reviewed articles were included (Fig. 1). Upon identification of the articles for review, we analyzed the enrollment number, inclusion criteria, purpose and outcomes of all reviews, which are presented in Table 4.

2.1. Histopathological criteria in pediatric adrenocortical carcinoma (ACC) & TP53

The most widely-used and valuable histopathological scoring criteria for predicting the behavior of a malignancy of the adreno-cortical is the so-called Weiss scoring system from the author, who originally identified some criteria to pick up malignant behavior in adrenocortical neoplasia [9,10]. Weiss criteria are most commonly utilized for distinguishing between benign and malignant lesions in adults ACT patients [9,10]. Weiss criteria consists of three main categories of parameters: structural (clearing of cells, diffuse pattern in architecture, and tissue necrosis), cytological (nuclear grade, mitoses/50 high power fields, and atypical mitoses), and invasion (venous invasion, sinusoidal invasion, and capsular infiltration) [10]. Histopathologic criteria have been associated to endocrine dysfunction, but compared with the adult population, ACC in children more often presents as hormonally functional neoplasia (e.g. virilization), while the most common manifestation of ACC in adults is Cushing's syndrome. The clinical difference in ACT between the two age groups suggests indeed two distinctive mechanisms of carcinogenesis [11]. Two multicenter retrospective analyses in pediatric ACT demonstrated that histological features and clinical behaviors were not consistent when Weiss criteria were applied in the pediatric population [12,13]. Therefore, Weiss criteria do not accurately predict clinical outcome and are not entirely applicable to pediatric ACC. Lack of definitive and reliable histopathological criteria for malignancy in the childhood and youth is probably the greatest

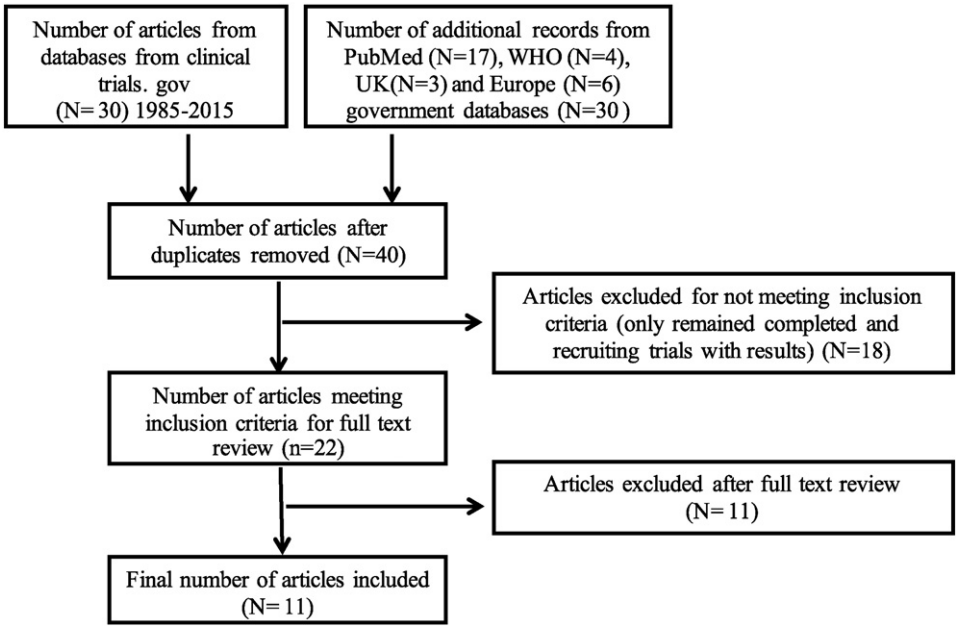

Fig. 1. Flow diagram of the literature review process for identifying studies on the clinical trials in Pediatric ACT (1985-2015).