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Mini Review

DICER1 Syndrome: A Cancer Predisposition Syndrome that can be First Diagnosed by the Pediatrician

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Abstract

DICER1 syndrome is an increasingly recognized cancer predisposition syndrome; inherited as an autosomal dominant with variable penetrance. Due to the pleiotropic nature of the syndrome and the fact that many of its tumor components are classified as benign and diagnosed during childhood; the likelihood that patients with DICER1 syndrome are first seen by a pediatrician or a neonatologist is pretty high. This article aims at raising the awareness of the general pediatricians about the DICER1 syndrome, its tumor constitutes that once diagnosed should signal referral to a specialized care team experienced in the management of children with inherited abilities to develop multiple cancers in their lifetime.

Keywords: *DICER1 Gene; Cancer Predisposition; Multinodular Goiter; Pleuropulmonary Blastoma; Cystic Nephroma; Ovarian Tumor*

Abbreviations

mRNA: Messenger RNA; CPS: Cancer Predisposition Syndrome; RISC: RNA Silencing Complex

Introduction

The genetic background of cancer is increasingly recognized [1]. It is estimated that at least 10% of pediatric cancers are due to an underlying cancer predisposition syndrome (CPS) with a threshold of 5% considered sufficient by the American Association for Cancer Research (AACR) to recommend screening [2]. Children with CPSs are prone to develop multiple cancers in their lifetime [3]. Some syndromes are characterized by the development of both benign and malignant tumors [4]. Early recognition of the genetic nature of the disorder, allows for the detection of various types of cancers at earlier stages and subsequently better outcomes [5].

DICER1 cancer predisposition syndrome is a good example of an autosomal dominant condition that renders the affected individual susceptible to a variety of benign and malignant conditions. The syndrome should be suspected in patients who have multiple relatives in their families with a history of benign thyroid disease particularly multinodular goiter [6]. Neonatologists are sometimes confronted with a newborn with lung or renal cysts discovered on the chest or abdominal radiographs done for other purposes [7]. Neonatal lung cysts can be the presenting feature of pleuropulmonary blastoma; the hallmark of the DICER1 syndrome [8].

Genetic background

The *DICER1* gene encodes the Dicer protein, which is widely expressed among tissues and is involved in cellular proliferation and differentiation [9,10]. The Dicer protein functions to control gene expression through the production of microRNA from cleaving precursor RNA molecules [11]. MicroRNAs in turn, block protein production by attaching to specific messenger RNA (mRNA) molecules thereby hindering mRNA translation through the miRNA silencing complex (RISC) [12]. The process finally leads to mRNA decay and inhibition of protein production [13].

Mutations in *DICER1* gene (14q32.13)

Germline loss of function mutation in the *DICER1* gene that was mapped to the 14p32.13 chromosome results in the tumor susceptibility syndrome "The DICER1 tumor predisposition syndrome" [14]. An atypical form of the Knudson two-hit hypothesis is applied here [15,16]. As every gene in the body has two alleles, if an individual was born with a mutant copy of one allele, he/she will require an additional second hit to the remaining normal allele later in life to develop cancer. In contrast, the individual who was born with normal both copies requires two hits in the cells of the particular tissue to develop a specific tumor type [17]. In the case of the DICER1 tumor susceptibility syndrome, the *DICER1* gene wild mutation results in loss of function that reduces by half the amount of the normal Dicer protein [18]. The second-hit is usually a highly specific missense mutation that is almost exclusively confined to the RNase IIIb domain of the *DICER1* gene [19]. The person whose gene has the double-hit mutation -who was born with an already mutant one copy- is prone to tumorigenesis more easily than the person who acquires both hits to the gene in a particular tissue later in life [20]. Another mechanism of mutation in the *DICER1* gene is through the loss of heterozygosity, however, this is rarely reported and usually confined to cases with pineoblastoma [21,22].

Encountering a patient with a likely DICER1 tumor susceptibility syndrome

Many tumors described in the DICER1 susceptibility syndrome are benign in nature, however, should raise the suspicion that the affected person might be having an underlying germline mutation that increases his/her susceptibility to developing multiple cancers later in life [23]. The syndrome implies many features especially multinodular goiter and thyroid hyperplasia [6,24]. Most prominently occurring in families where multiple relatives are diagnosed with thyroid disease [25]. Data is emerging on the direct relationship between the DICER1 syndrome and thyroid carcinoma [26] with the DICER1-mutated papillary subtype considered a distinct entity of low-risk malignancy [27].

Pediatricians, neonatologists, and general practitioners are likely the first physicians faced with infants and young children with cysts in the lungs or kidneys through evaluation of chest radiographs or abdominal ultrasound done for investigating other conditions or rarely due to respiratory or renal compromise. The infant with lung cysts may harbor a pathogenic germline variant in the *DICER1* gene that may be his earliest manifestation of the syndrome [28]. A variety of cystic lung conditions had been reported in association with the DICER1 syndrome. Characteristically, lung cysts described in the DICER1 syndrome are multiseptated and often bilateral. Shultz., *et al.* described the pathogenic germline mutations in the RNase IIIb domain of the *DICER1* gene that are causative of pleuropulmonary blastoma [29]. Clinical and radiographic data can distinguish pleuropulmonary blastoma from Congenital Pulmonary Airway Malformation (CPAM) [30]. The latter may progress into pleuropulmonary blastoma by acquiring *DICER1* mutation [31]. Germline *DICER1* gene mutation was reported to occur in patients diagnosed with Well-Differentiated Fetal Adenocarcinoma (WDFA) of the lung [32]. Including the possibility of an underlying *DICER1* germline mutation among the differential diagnosis of a patient with cystic lung allows for earlier identification of the disease and therefore better outcomes.

Similarly, pediatricians may encounter an infant with abdominal swelling due to a unilateral -or bilateral-multilocular cystic renal mass. There is a high probability for the mass to be cystic nephroma due to germline mutation in the *DICER1* gene [33]. Therefore, it is

of crucial importance to understand the genetic nature of the DICER1 syndrome in order to allow for early referral to specialized cancer centers with a multidisciplinary team approach that includes genetic counseling and screening testing. Surveillance protocols are now published for early detection of the DICER1 syndrome-related malignancies with particular emphasis on early detection of ovarian sex cord-stromal tumors, pituitary blastoma, and pineoblastoma, genitourinary embryonal rhabdomyosarcoma among others [23,34]. It is estimated that close to twenty percent of the individuals who are *DICER1* gene mutant carries will develop a neoplasm by age fifty [35].

Conclusion

DICER1 syndrome is a cancer predisposition syndrome that increases the individual's susceptivity to develop multiple benign and malignant tumors in his lifetime. General pediatricians and neonatologists are likely the first physicians to deal with patients with cystic disease in the lungs or kidneys. Lung cysts can be a type 1 pleuropulmonary blastoma, similarly, a renal mass with cystic components can be a cystic nephroma resulting from an underlying germline mutation in the DICER1 gene. Early recognition and direct referral to a specialized cancer center with experts in handling patients with cancer predisposition syndromes improve long-term patient outcomes.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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