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Commentary

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Genetic Diagnosis of Primary Adrenal Insufficiency in Children: A Paradigm Change

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Abbreviations: AHC, adrenal hypoplasia congenita; PAI, primary adrenal insufficiency; STAR, steroidogenic acute regulatory protein.

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Primary adrenal insufficiency (PAI) is defined by the impaired synthesis and secretion of cortisol, with or without deficiency of aldosterone and androgens. The type and extent of the hormone deficiency is determined by the underlying cause of adrenal insufficiency. PAI is a rare disease with a reported prevalence of 100 to 140 cases per million and an incidence of 4 to 6 per million per year in adults. However, the incidence of PAI in children is not well established. Adrenal crisis is a life-threatening condition that requires immediate treatment and is associated with high mortality [1]. In adults, PAI is mainly caused by acquired etiologies, autoimmune or infectious. Etiologies of PAI in children can be classified as congenital adrenal hyperplasia, autoimmune, metabolic disorders (Wolman disease, Zellweger spectrum, mitochondrial disorders, adrenoleukodystrophy), physical damage of adrenal glands or as unknown etiologies (after evaluation of clinical or hormone features). In contrast to adults, genetic defects are more prevalent in children. Congenital adrenal hyperplasia is the most frequent cause of PAI in pediatric patients, with 21-hydroxylase deficiency being the most frequent enzymatic defect [1].

In recent years, the genetic causes of PAI have significantly expanded [2]. Besides defects in genes involved in adrenal steroidogenesis and metabolic disorders, new genetic etiologies demonstrated the importance of genes involved in adrenal development to the pathogenesis of PAI. Pathogenic variants in the *NR0B1/DAX1* gene, a coregulator of transcription factor SF1, cause X-linked adrenal hypoplasia congenita (AHC), the most frequent form of AHC [3]. The classic clinical features of X-linked AHC include primary salt-losing adrenal insufficiency, hypogonadotropic hypogonadism, and infertility. Pathogenic variants in *SF1* are associated with testicular dysgenesis, severe hypospadias, and infertility in 46,XY individuals or primary ovarian insufficiency in 46,XX women, but only rare cases develop PAI. Moreover, PAI can be part of syndromes associated with intrauterine growth restriction, AHC, and sexual development disorders, such as IMAGe syndrome (defect of the *CDKN1C* gene), MIRAGE syndrome (*SAMD9* gene), and IMAGe-like syndrome (*POLE1* gene) [4].

Steroidogenic acute regulatory protein (STAR) and cytochrome P450 side-chain (P450scc, encoded by CYP11A1) are involved in the initial steps of steroidogenesis. Severe

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deficiency of *STAR* or *CYP11A1* promotes salt-losing adrenal insufficiency and cortisol insufficiency very early in life [5]. In addition to this classic phenotype, children with partial deficiency of *STAR* or *CYP11A1* (nonclassic) can present with PAI mainly with glucocorticoid deficiency, not requiring mineralocorticoid replacement. Furthermore, isolated glucocorticoid deficiency can also be caused by adrenocorticotropin resistance (*MC2R*, *MRAP*, *MCMR*, and *AAAS* genes) or deficiency of mitochondrial reactive oxygen species detoxification (*NNT* and *TXNRD2* genes) [4].

In this issue of the *Journal of the Endocrine Society* (JES), Buonocore et al [6] investigated genetic causes of PAI of unknown etiology in 155 children. Patients with congenital adrenal hyperplasia, autoimmune, or metabolic disease were excluded from the cohort. Since 2013, a next-generation sequencing approach was employed to identify the genetic diagnosis in 75 of 155 patients. A genetic diagnosis was identified in 66.5% of the patients: *MC2R* 19.4%, *NR0B/DAX1* 7.7%, *CYP11A1* 7.7%, *AAAS* 7.1%, *NNT* 6.5%, *MRAP* 4.5%, *TXNRD2* 4.5%, *STAR* 3.9%, *SAMD9* 3.2%, *CDKN1C* 1.3%, and *NR5A1/SF1* 0.6%. No genetic diagnosis was found in 30.3% of the cohort, and steroid replacement treatment was gradually withdrawn in 5 (3.2%) children. This retrospective observational study represents the largest cohort of children with PAI of unknown etiology investigated for genetic causes [6]. Second, this study has a strong translational impact, since achieving a genetic diagnosis in the majority of the cohort has great importance to patient care. A recent Turkish study of 77 children with PAI of unknown etiology achieved a genetic diagnosis in 82% of the patients, but a higher consanguinity was found in the kindreds [7].

Interestingly, a predominance of boys was observed in this study, which persisted even after patients' X-linked AHC were removed. This male-sex predominance was also higher among patients without a genetic diagnosis [6]. The authors suggested 2 hypotheses that require further investigation: 1) an X-linked phenomenon, such as a new genetic cause or alteration in a regulatory region of a key gene such as *DAX1*; and 2) sex differences in adrenal function, increasing the likelihood of diagnosing PAI in boys.

Age of presentation, treatment, and associated clinical features can provide some clues to predict genetic diagnosis [2, 4]. Hormone profile (increased adrenocorticotropin and low cortisol levels, abnormal cortisol response to stimulation, with or without mineralocorticoid insufficiency) is similar in most cases. X-linked AHC usually affects boys with salt loss in early life. Glucocorticoid insufficiency (*MC2R* or *MRAP*) often presents with prolonged neonatal jaundice or hypoglycemic convulsions. Children with *MRAP* defects present with PAI in early life, whereas patients with triple A syndrome are more often diagnosed in mid-childhood. Moreover, nonclassic *CYP11A1* or *STAR* deficiency can present in childhood with ketotic hypoglycemia. However, it should be emphasized that genetic testing was essential to define the cause of PAI in most cases [6]. Because more than 20 genes have been associated with genetic causes of PAI, a next-generation sequencing approach (target panel or exome) is the most cost-effective approach to perform the genetic analysis.

Patients with PAI have an increased rate of overall and cardiovascular mortality [1]. Reaching a genetic diagnosis for PAI can have important implications for a precocious diagnosis, preventing a salt-loss crisis in early life and other life-threatening complications, and enabling genetic counseling, personalizing hormone replacement therapy, and surveillance of associated clinical features. Indeed, it has been previously demonstrated that genetic diagnosis at an early stage in patients with germline *SDHx* or *VHL* defects had a positive effect on management and clinical outcome, including survival [8].

In conclusion, this study published in *JES* demonstrated that a genetic diagnosis was achieved in the majority of children with PAI of unknown etiology. This finding represents a paradigm change in the management of pediatric PAI, supporting the recommendation that all children with PAI should undergo genetic investigation. After exclusion of frequent forms of congenital adrenal hyperplasia, metabolic, or autoimmune disorders, a next-generation sequencing approach should be used to search for a genetic etiology. Long-term follow-up studies are now required to analyze the positive impact of genetic diagnosis in the outcome of children with PAI.

Additional Information

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