Review article

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Congenital lipoid adrenal hyperplasia

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Congenital lipoid adrenal hyperplasia (lipoid CAH) is the most fatal form of CAH, as it disrupts adrenal and gonadal steroidogenesis. Most cases of lipoid CAH are caused by recessive mutations in the gene encoding steroidogenic acute regulatory protein (StAR). Affected patients typically present with signs of severe adrenal failure in early infancy and 46,XY genetic males are phenotypic females due to disrupted testicular androgen secretion. The StAR p.Q258X mutation accounts for about 70% of affected alleles in most patients of Japanese and Korean ancestry. However, it is more prevalent (92.3%) in the Korean population. Recently, some patients have been showed that they had late and mild clinical findings. These cases and studies constitute a new entity of 'nonclassic lipoid CAH'. The cholesterol side-chain cleavage enzyme, P450scc (*CYP11A1*), plays an essential role converting cholesterol to pregnenolone. Although progesterone production from the fetally derived placenta is necessary to maintain a pregnancy to term, some patients with P450scc mutations have recently been reported. P450scc mutations can also cause lipoid CAH and establish a recently recognized human endocrine disorder.

Keywords: Steroidogenic acute regulatory protein, Lipoid congenital adrenal hyperplasia, Cholesterol side-chain cleavage enzyme

Introduction

Congenital lipoid adrenal hyperplasia (lipoid CAH), the most fatal form of adrenal hyperplasia, seriously disrupts adrenal and gonadal steroidogenesis by a defect in the conversion of cholesterol to pregnenolone[1]. Affected patients show salt loss from impaired mineralocorticoid and glucocorticoid synthesis[2]. Deficient fetal testicular steroidogenesis in patients with a 46,XY karyotype results in phenotypically female external genitalia. The defect in lipoid CAH is mainly in the steroidogenic acute regulatory protein (StAR)[3,4], which promotes entry of cholesterol into mitochondria, where it becomes the substrate for the cholesterol side-chain cleavage enzyme, P450scc[1,5]. P450scc deficiency will also inhibit placental progesterone synthesis and probably interrupts pregnancy, although rare P450scc mutations have been reported in children with adrenal insufficiency[6-9]. In steroidogenic disorders, such as steroid 21-hydroxylase deficiency, a spectrum of clinical findings results from different missense mutations. However, the clinical findings are remarkably similar in lipoid CAH. Most patients have female external genitalia regardless of chromosomal sex and have evidence of salt loss in the first year of life and usually within the first 2 months[3,4,10-13]. Some patients have shown late and mild clinical findings[14]. These cases and studies constitute a new entity of "nonclassic lipoid CAH".

Steroid biosynthesis

Cholesterol is the precursor for steroidogenesis and the initial rate-limiting step is the conversion of cholesterol to pregnenolone[1]. The acute stimulation of steroidogenesis is accomplished at the level of cholesterol import into mitochondria, which is promoted by

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StAR[1,5]. After cholesterol uptake into the mitochondrion, it is cleaved by the P450scc enzyme. This single enzyme, encoded by a single gene (*CYP11A1*), catalyzes three distinct chemical reactions on a single active site: cholesterol sequentially undergoes 20-hydroxylation, 22-hydroxylation, and scission of the 20, 22 C-C bond to produce pregnenolone[15,16]. P450scc can only function within mitochondria[17]; thus, transport of cholesterol to the inner mitochondrial membrane by StAR is a crucial step in steroidogenesis. Several enzymes stimulate chronically over hours to weeks including a series of cytochrome P450 enzymes. These enzymes are categorized into two types according to their localization and electron transport system. Mitochondrial (type I) cytochrome P450 enzymes include P450scc, 11β-hydroxylase, and aldosterone synthase, and microsomal (type II) cytochrome P450 enzymes include 17α-hydroxylase, 21-hydroxylase, and P450 aromatase[5].

A clinical defect of all steroidogenesis was first reported in 1955[18], and several studies of affected tissue indicated defective conversion of cholesterol to pregnenolone[2,19,20], so this disorder was thought to represent an enzymatic defect originally termed '20, 22 desmolase deficiency'[1]. However, studies of DNA from affected patients revealed that the *CYP11A1* gene encoding P450scc was normal[21-24], and in 1995 this disease was more properly termed 'congenital lipoid adrenal hyperplasia (lipoid CAH)', and it was caused by mutations in the gene encoding StAR[3,25].

StAR deficiency

Lipoid CAH is a rare autosomal recessive disorder that severely inhibits the synthesis of all adrenal and gonadal steroids[1]. A severe defect in fetal testicular biosynthesis is evident because affected 46,XY genetic males are born with all female external genitalia, reflecting an absence of testosterone synthesis between 6 and 12 weeks of gestation[26]. The adrenal glands are enlarged with cholesterol ester deposits at birth. Affected infants have low but measurable levels of steroid hormones, but they soon die from glucocorticoid and mineralocorticoid deficiency if hormone treatment is not initiated[26]. Although StAR is essential for an acute and maximal steroidogenic response, there are also low levels of StAR-independent steroidogenesis[3,4]. The demonstration of StAR-independent steroidogenesis led to the formulation of the two-hit model of lipoid CAH[4]. The first hit is the mutation in the StAR gene, ablating StAR-dependent steroidogenesis but permitting StAR-independent steroidogenesis to persist[4]. This enables normal placental steroidogenesis and term gestation and also explains the low, but detectable, levels of steroid hormones seen in the sera of patients with lipoid CAH during the first month of life[2,4]. This, in turn, explains why infants with untreated lipoid CAH can survive without treatment for several months[2,4,10], whereas patients with other forms of salt wasting CAH do not. However, these steroid hormone levels are too low to suppress secretion of adrenocorticotropic hormone (ACTH), gonadotropins, and angiotensin II[26]. These tropic hormones stimulate cellular uptake of low density lipoprotein-cholesterol and increase production of cholesterol from acetate, resulting in the accumulation of cholesterol esters, which finally destroy cells either via physical enlargement with droplets of cholesterol esters or by a chemical action of cholesterol oxidation products, or both[4]. This second hit disrupts the low levels of StAR-independent steroidogenesis, leading to undetectable levels of steroid in older children with lipoid CAH[4]. Fetal ovaries do not express the steroidogenic enzyme genes and, thus, do not make steroids[27]. Unlike the testes and adrenal glands, the ovaries only start to make steroid hormones at the onset of puberty[26]. Thus, the ovaries of 46,XX females affected with lipoid CAH do not receive the second hit until the onset of puberty, when luteinizing hormone stimulates low-levels of StAR-independent steroidogenesis[26]. Each month another follicle is recruited and stimulated by gonadotropins, presenting spontaneous breast development in affected girls[26]. However, gonadotropin stimulation quickly results in cholesterol accumulation in these cells (the second hit in lipoid CAH), so the later phase of ovarian steroidogenesis, secretion of large amounts of progesterone, does not occur[28,29]. Follicles that are not recruited remain unstimulated and constitute a reservoir of steroidogenic cells undamaged by the second hit of lipoid CAH, so a new undamaged follicle is recruited with each regular cycle, and estrogen is produced leading to cyclic uterine estrogen withdrawal bleeding that resembles a normal menstruation, but there is no progesterone, so these cycles are anovulatory[26].

Lipoid CAH has been reported in most ethnic groups but is common among the Japanese, Korean, and Palestinian Arab populations[1,3,4,10,11,13,29-32]. To date, forty-eight different mutations in the *StAR* gene have been reported in various ethnic groups (http://www.hgmd.org/). The incidence of certain mutations is very high in specific ethnic groups. Genetic clusters consistently contain the p.Q258X mutation in the Japanese and Korean populations[10,30], the p.R182L mutation in Palestinian Arabs[4], the p.R182H mutation in eastern Saudi Arabians[13], and the p.L260P mutation in the Swiss population[11]. Most patients with lipoid CAH have female external genitalia regardless of genetic sex and have evidence of salt loss in the first year of life[1]. Recently, some patients have showed that they had late and mild clinical findings with male external genitalia[14]. These unique clinical courses, which are consistent with the demonstrated partial functional activity of each mutation, constitute a new entity called "nonclassic lipoid CAH", indicating that the clinical finding of StAR mutations is substantially broader than had been appreciated previously[14]. Nonclassic lipoid CAH is a new form of nonautoimmune Addison disease that presents with or without salt loss[14].

P450scc deficiency

Placental production of progesterone is essential to prevent uterine contractility, permitting a pregnancy to be maintained. Thus, human pregnancy relies on progesterone from the mother's corpus luteum during the first trimester. Furthermore

there is a 'luteo-placental shift' to production of progesterone by the placental fetal syncytiotrophoblasts[33]. In the pregnancies of some animals, such as the rabbit and rodent, progesterone is supplied by the corpus luteum during pregnancy, so deletion of P450scc remains compatible with term gestation[33]. Thus, it was thought that the interruption of progesterone synthesis by the human placenta would result in second trimester spontaneous abortion[34], but several cases of severe P450scc mutations have now been reported[6-9,35]. P450scc deficiency is a novel, rare disorder that can present as acute adrenal insufficiency at any time from infancy to early childhood[35]. In all cases, ACTH and plasma renin activity are grossly elevated and adrenal steroids are inappropriately low or absent; the 46,XY patients have female external genitalia, sometimes with clitoromegaly[35]. In contradiction to the huge adrenal enlargement typically seen in lipoid CAH caused by mutations in StAR[2], no patients with a P450scc deficiency has been reported to have adrenal hyperplasia[36]. Although a small number of patients with StAR mutations have normal-sized adrenal glands[14,32], this may be useful to distinguish these disorders. Additional cases, particularly those studied hormonally during pregnancy, may present further information about the hormonal control of childbirth and elucidate the pathophysiology of P450scc deficiency.

Korean patients with StAR deficiency

The p.Q258X mutation is associated with about 70% of affected Japanese and Korean patients[37]. However, it is more prevalent (92.3%) in Korean alleles[38]. These results suggest that the genetic defect in the *StAR* gene in Korean patients with lipoid CAH is highly homogeneous, probably reflecting a founder effect[38]. The majority of patients with lipoid CAH carrying the p.Q258X mutation typically show severe adrenal failure within the first 2 months of life[3,10,30]. It has been demonstrated that p.Q258X is a null mutation, resulting in elimination of StAR function[3,4]. Kim et al.[38] found that the gene frequency for the p.Q258X mutation in the Korean population was ~1/500, with a 1/250 carrier frequency. The confidence limits of the gene frequency for the mutant allele are 0.5–8.0 among 1,000 alleles. Therefore, the carrier frequency could be lower (1/1,000) or higher (16/1,000)[38]. However, the estimated incidence could be inaccurate due to insufficient sample size[30]. The p.Q258X mutation is the most commonly found StAR gene mutation in Korean patients with lipoid CAH. Additionally, other mutations (p.R272H, p.R217fsX48, p.V187M, p.R182C, p.R182H, p.L98R, and c.745-6_810del) have been reported infrequently[38].

Differences between StAR and P450scc deficiency

The clinical and laboratory findings in patients with mutations in the *StAR* or *CYP11A1* genes are essentially indistinguishable, and their treatment is the same; hormonal replacement therapy with physiological doses of glucocorticoids and mineralocorticoids[36]. Most patients with lipoid CAH have massive adrenal enlargement; however, small adrenal glands have rarely been reported in classic lipoid CAH[32]. In contrast, none of the patients with *CYP11A1* mutations reported to date has had adrenal enlargement[36]. However, an ultrasonogram may not be as sensitive as computed tomography scanning, and the ultrasound was conducted in the first week of life when the adrenal glands may not yet be enlarged. Therefore, clinical, imaging and hormonal findings alone may not distinguish between P450scc and StAR deficiency; gene sequencing is the only definitive diagnostic method[36]. Discriminating these two very similar diseases permits prenatal diagnosis and genetic counseling[36].

Conclusions

Lipoid CAH is the most fatal form of CAH and is common in Japan and Korea. Most cases of lipoid CAH are caused by recessive mutations in the *StAR* gene. To date, 48 different mutations in the *StAR* gene have been reported in various ethnic groups. The incidence of certain mutations is very high in specific ethnic groups, and the p.Q258X mutation is hot spot in Korean alleles. Some patients with lipoid CAH have shown late and mild clinical findings. These cases constitute a new entity of 'nonclassic lipoid CAH'. Additionally, P450scc mutations can also cause lipoid CAH and establish a recently recognized human endocrine disorder. The clinical and laboratory findings in patients with mutations in the *StAR* or *CYP11A1* genes are essentially indistinguishable. Clinical and hormonal findings alone may not distinguish between P450scc and StAR deficiency, and gene sequencing is the only definitive diagnostic method.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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