REVIEW

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Latest Insights on the Etiology and Management of Primary Adrenal Insufficiency in Children

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Abstract

Primary adrenal insufficiency (PAI) is a heterogeneous group of disorders characterized by an impaired production of cortisol and other steroid hormones by the adrenal cortex. Most of the causes of PAI in childhood are inherited and monogenic in origin and are associated with significant morbidity and mortality whenever the diagnosis and treatment is delayed. Therefore, early and accurate diagnosis would allow appropriate management for the patients and genetic counselling for the family. Congenital adrenal hyperplasia accounts for most cases of PAI in childhood, followed by abnormalities in the development of the adrenal gland, resistance to adrenocorticotropin hormone action and adrenal destruction. In recent years, the use of genome-wide, next-generation sequencing approaches opened new avenues for identifying novel genetic causes in the PAI spectrum. Understanding the genetic basis of adrenal disorders is key to develop innovative therapies for patients with PAI. The promising progress made in congenital adrenal hyperplasia treatment brings new perspectives for personalized treatment in children with PAI. The aim of this review is to characterize recent advances in the genetics and management of PAI in children.

Keywords: Primary adrenal insufficiency, children, etiology, treatment

Introduction

Primary adrenal insufficiency (PAI) is a relatively rare but potentially lethal clinical condition in which the adrenal cortex cannot produce adequate amounts of steroid hormones, primarily cortisol, but may also include impaired production of aldosterone and adrenal sex steroids. Recent molecular advances have expanded our knowledge of the etiologies of PAI. However, its diagnosis may be missed or delayed unless an illness or stress precipitates a severe cardiovascular collapse resulting in acute adrenal crisis. Early recognition of the clinical findings and treatment with glucocorticoids and rehydration with intravenous fluids, with or without mineralocorticoids and salt, are life-saving while attempts to confirm the diagnosis with extensive work-up are ongoing. Delay in treatment may result in disastrous clinical outcomes.

This review mainly focuses on the recent advances in the etiology, clinical manifestations and management of PAI of genetic origin in children.

Etiology

PAI in children may arise from abnormalities in the development of adrenal gland, impaired steroidogenesis, resistance to adrenocorticotropin hormone (ACTH) action [familial glucocorticoid deficiency (FGD)] or adrenal destruction. In contrast to the predominance of autoimmune etiologies in adults, most causes of PAI in childhood are inherited and monogenic in origin (1,2,3,4). Table 1 summarises the aetiologies of inherited PAI in children.

Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH), which occurs in 1 in 10.000-18.000 live births, accounts for most cases of PAI in childhood (5). CAH represents a group of autosomal recessive disorders associated with deficiencies in the enzymes and cofactor proteins required for cortisol biosynthesis (6). Cortisol deficiency increases ACTH production that subsequently leads to adrenocortical hyperplasia and accumulation of the upstream precursor steroids above the enzyme deficiency. The accumulated upstream steroids and their urinary metabolites present the

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Table 1. Aetiologies of inherited primary adrenal insufficiency in children

Condition/deficiency	Gene	OMIM	Associated clinical signs and symptoms
Impaired steroidogenesis			
Impaired cholesterol transport			
Steroidogenic acute regulatory protein (congenital lipoid adrenal hyperplasia)[±]	*StAR*	201710	46,XY DSD, gonadal insufficiency
Steroidogenic enzyme / co-factor deficiency causing congenital adrenal hyperplasia			
21α-hydroxylase deficiency	*CYP21A2*	201910	46,XX DSD, hyperandrogenism
11β-hydroxylase deficiency	*CYP11B1*	202010	46,XX DSD, hyperandrogenism, arterial hypertension
17α-hydroxylase deficiency	*CYP17A1*	202110	46,XY DSD, arterial hypertension, gonadal insufficiency
P450 oxidoreductase deficiency	*POR*	201750	46,XX and 46,XY DSD, gonadal insufficiency, bone malformations, affects all endoplasmic CYP450 enzyme functions
3β-hydroxysteroid dehydrogenase type 2	*HSD3B2*	201810	46,XX and 46,XY DSD, premature adrenarche, hyperandrogenism in female
P450 side-chain cleavage enzyme (P450scc)	*CYP11A1*	118485	46,XY DSD, gonadal insufficiency
Defects in cholesterol synthesis or metabolism			
Smith-Lemli Opitz disease	*DHCR7*	270400	Mental retardation, craniofacial malformations, growth failure
Abetalipoproteinemia[Ω]	*MTP*	200100	Ataxia, retinopathy, acanthocytosis, malabsorption of fat
Familial hypercholesterolemia[Ω]	*LDLR*	143890	Tendon xanthomas, xanthelasma, corneal arcus
Sitosterolemia (phytosterolemia)[Ω]	*ABCG5* *ABCG8*	210250	Short stature, gonadal failure, xanthomas, hemolytic anemia, arthritis, accelerated atherosclerosis and premature cardiac death
Adrenal dysgenesis/hypoplasia			
Without syndromic features			
X-linked adrenal hypoplasia congenital	*NR0B1 (DAX1)*	300200	Hypogonadotropic hypogonadism in boys. In some cases gonadotropin independent precocious puberty
Xp21contiguous gene deletion syndrome (5% of cases)	Deletion of genes for Duchenne muscular dystrophy, glycerol kinase, and NR0B1		Duchenne muscular dystrophy, glycerol kinase deficiency, psychomotor retardation (if deletions extend to the *IL1RAPL1* gene)
Adrenal hypoplasia steroidogenic factor-1 deficiency	*NR5A1 (SF1)*	184757	46,XY and 46,XX sex reversal, 46,XY DSD, 46,XX DSD, primary ovarian failure, spermatogenic failure
With syndromic features			
IMAGe syndrome	*CDKN1C*	300290	Intrauterine growth retardation, metaphyseal dysplasia, adrenal insufficiency, genital anomalies
MIRAGE syndrome	*SAMD9*	617053	Myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, and enteropathy
Pallister-Hall syndrome	*GLI3*	165240	Hypothalamic hamartoblastoma, hypopituitarism, imperforate anus, mesoaxial and postaxial polydactyly, laryngotracheal cleft, bifid epiglottis
Meckel syndrome	*MKS1*	249000	Central nervous system malformation (occipital encephalocele), polycystic kidney, hepatic fibrosis, polydactyly
Pena-Shokeir syndrome 1	*DOK7*	208150	Arhrogryposis, fetal akinesia, intrauterine growth retardation, cystic hygroma, pulmonary hypoplasia, cleft palate, cryptorchidism, cardiac defects, camptodactyly, polyhydramnios, intestinal malrotation, pterygiums in extremities

Table 1. Continue

Condition/deficiency	Gene	OMIM	Associated clinical signs and symptoms
Pseudotrisomy 13	*RAPSN*	264480	Holoprosencephaly, facial abnormalities, postaxial polydactyly
Hydrolethalus syndrome	*HYLS1*	236680	Prenatal-onset severe hydrocephalus, polydactyly, micrognathia, abnormal genitalia, congenital heart and pulmonary defects,
Galloway-Mowat syndrome	*WDR73*	251300	Early-onset severe encephalopathy, severe epilepsy, nephrotic syndrome, microcephaly, hiatal hernia
Chromosomal abnormalities	Tetraploidy, triploidy, trisomy 18, trisomy 21, 5p dup, and 11q syndrome		Often associated with central nervous system abnormalities and prenatal-onset growth retardation
ACTH resistance			
Familial glucocorticoid deficiency type 1	*MC2R*	202200	*Generally* isolated glucocorticoid deficiency without mineralocorticoid deficiency, tall stature, subclinical hypothyroidism, characteristic facial features, such as hypertelorism, medial epicanthus and frontal bossing
Familial glucocorticoid deficiency type 2	*MRAP*	607398	*Generally* isolated glucocorticoid deficiency without mineralocorticoid deficiency
Adrenal destruction			
Impaired redox homeostasis			
Nuclear envelope defects			
Triple A syndrome (Allgrove syndrome)	*AAAS*	231550	Alacrimia, achalasia, dysfunction of autonomic nervous system; additional symptoms, including neurologic impairment, deafness, mental retardation, hyperkeratosis
Mitochondrial defects			
Nicotinamide nucleotide transhydrogenase deficiency	*NNT*	614736	*Generally* isolated glucocorticoid deficiency without mineralocorticoid deficiency, subclinical hypothyroidism, insulin-dependent diabetes mellitus
Thioredoxin reductase deficiency[§]	*TXNRD2*	606448	Isolated glucocorticoid deficiency
Glutathione peroxidase deficiency + peroxiredoxine deficiency*	*GPX1 + PRDX3*		A single patient with homozygous gene defects in both genes was described. Patient had isolated glucocorticoid deficiency
Defects in complex lipid metabolism			
a) Peroxisomal defects			
X-linked adrenoleukodystrophy (X-linked ALD)	*ABCD1* *ABCD2*	300100 300371 601081	Progressive neurodegeneration, cognitive and behavioral changes, progressive loss of hearing and vision; dementia, spasticity, seizure
Neonatal adrenoleukodystrophy (autosomal recessive)	*PEX1*	601539	Severe hypotonia, seizures and encephalopathy, blindness and deafness, hepatic dysfunction, peroxysomal agenesis
Zellweger syndrome	*PEX1, 2, 3, 5, 6, 12, 14, 26*	214100	Severe neuromotor and growth retardation, hypotonia, deafness, blindness, craniofacial abnormalities, hepatovmegaly, stippled epiphysis, genitourinary anomalies, infants occasionally mistaken as having Down syndrome
Refsum disease	*PHYH, PEX7*	266500	Multiple epiphyseal dysplasia, cardiomyopathy, anosmia, retinitis pigmentosa, neuropathy, deafness, ataxia, ichthyosis

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Table 1. Continue

b) Lysosomal defects			
Wolman disease (lysosomal acid lipase deficiency, cholesterol ester storage disease)	*LIPA*	278000	Diffuse punctate adrenal calcification, xanthomatous changes in liver, adrenals, spleen, lymph nodes, bone marrow, small intestine, lungs and thymus and slight changes in skin, retina, and central nervous system
c) Endoplasmic reticulum defects			
Sphingosine-1-phosphate lyase deficiency	*SGPL1*	603723	Steroid-resistant nephrotic syndrome, ichthyosis, lymphopenia, neurological defects, primary hypothyroidism, cryptorchidism
Autoimmune destruction			
Isolated autoimmune adrenalitis	Association with CLTA-4, HLA-DR3, HLA-DR4, HLA-B8 *BACH2*	-	-
Autoimmune polyglandular syndromes (APS)			
APS type 1	AIRE		Chronic mucocutaneous candidiasis, hypoparathyroidism, other autoimmune disorders, rarely lymphomas
APS type 2	Association with HLA-DR3, CTLA-4		Hypothyroidism, hyperthyroidism, premature ovarian failure, vitiligo, type 1 diabetes mellitus, pernicious anemia
APS type 4	Association with HLA-DR3, CTLA-4 BACH2		Other autoimmune diseases, excluding thyroid disease or diabetes (unusual in children)
Miscellaneous			
DNA repair defects	*MCM4*[¥]	609981	Natural killer cell deficiency, short stature, microcephaly, recurrent viral infections, chromosomal breakage, susceptibility for neoplastic lesions
Bioinactive ACTH*	*POMC*		Signs and symptoms of POMC deficiency (obesity and red hair), high ACTH and low cortisol. Bioinactive but immunoreactive ACTH
Mitochondrial diseases			
Kearns-Sayre syndrome	Mitochondrial DNA deletions, *MTTL1*	530000	Progressive external ophthalmoplegia, ptosis, retinal degeneration, and cardiac conduction defects, microcephaly, other endocrinopathies, lactic acidosis, neuropathy, myopathy, ragged-red fibers seen on muscle biopsy
Mitochondrial DNA polymerase deficiency	*POLG1*	203700	Infantile epilepsy, metabolic strokes, chronic ataxia, neuropathy, and ophthalmoplegia, type I diabetes, hypothyroidism and psychiatric problems
Impaired mitochondrial disulfide relay system	*GFER*	613076	Encephalomyopathy, congenital cataracts, hypotonia, developmental delay and sensorineural hearing loss, lactic acidosis, respiratory failure
MELAS syndrome	*MTTL1, MTTQ, MTTH, MTTK, MTTC, MTTS1-2, MTND1, 5, 6*	540000	Mitochondrial myopathy, encephalopathy, lactic acidosis, *stroke-like episodes*
Impaired complex I assembly	*NDUFAF5*	252010	Agenesis of the corpus callosum and ventricular septation, congenital left diaphragmatic hernia and lactic acidosis

Table 1. Continue

Impaired translation	*MRPS7, QRSL1*	611974, 617209	Sensorineural deafness, primary ovarian failure, progressive hepatic and renal failure and lactic acidemia
Pearson syndrome	Contiguous gene deletion/ duplication of several mtDNA genes	557000	Low birth weight, failure to thrive, sideroblastic anemia, exocrine pancreatic dysfunction

±Mild defects may present like familial glucocorticoid deficiency (known mutations of StAR causing non-classic deficiency are p.R192C, p.R188C), ΩAsssociated with mild biochemical cortisol deficiency but not clinically significant adrenal failure, §Described only in seven individuals from a consanguineous Kashmiri kindred, to date, ¥Described only in the Irish traveler population, to date, *Described in a single patient

StAR: steroidogenic acute regulatory protein, *CYP21A2*: cytochrome P450, family 21, subfamily A, polypeptide 2, CYP11B1: cytochrome P450, family 11, subfamily B, polypeptide 1, CYP17A1: cytochrome P450, family 17, subfamily A, polypeptide 1, POR: cytochrome P450, oxidoreductase, HSD3B2: 3β-hydroxysteroid dehydrogenase 2, CYP11A1: cytochrome P450, family 11, subfamily A, polypeptide 1, DHCR7: 7-dehydrocholesterol reductase, MTP: microsomal triglyceride transfer protein, LDLR: low density lipoprotein receptor, ABCG8: ATP-binding cassette, subfamily G, member 8, NR0B1: nuclear receptor subfamily 0, group B, member 1, DAX1: dosage sensitive sex reversal, adrenal hypoplasia congenita, critical region on X chromosome, gene 1, NR5A1: nuclear receptor subfamily 5 group A member 1, SF1: steroidogenic factor 1, CDKN1C: cyclin dependent kinase inhibitor 1C, SAMD9: sterile alpha motif domain-containing protein 9, GLI3: gene responsible for Greig cephalopolysyndactyly syndrome, MKS1: gene responsible for Meckel syndrome, type 1 and Bardet-Biedl syndrome type 13, DOX7: docking protein 7, RAPSN: receptor associated protein of the synapse, HYLS1: hydrolethalus syndrome protein 1, WDR73: WD repeat domain 73, MC2R: melanocortin 2 receptor, MRAP: melanocortin 2 receptor accessory protein, AAAS: achalasia-alacrima-addisonianism, NNT: nicotinamide nucleotide transhydrogenase, TXNRD2: thioredoxin reductase 2, GPX1: glutathione peroxidase 3, PRDX3: peroxiredoxin 3, ABCD1: ATP-binding cassette, subfamily D, member 1, PEX: peroxisome biogenesis factor, PHYH: phytanoyl-CoA hydroxylase, LIPA: lipase A, SGPL1: sphingosine-1-phosphate lyase, BACH2: BTB and CNC homology 2, AIRE: autoimmune regulator, MCM4: minichromosome maintenance complex component 4, POMC: proopiomelanocortin, POLG1: polymerase, DNA, gamma-1: GFER1: growth factor, ERV1-like, NDUFAF5: NADH dehydrogenase (ubiquinone) complex I, assembly factor 5, MRPS7: mitochondrial ribosomal protein S7, QRSL1: glutaminyl t-RNA-synthase like protein 1, MIRAGE: myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital

biochemical fingerprints for the localization of the defect (Figure 1). Additionally, these steroid precursors are generally diverted to androgen producing alternate pathways leading to androgen excess. The accumulation of certain steroid precursors enable differentiation of steroidogenic enzyme deficiencies (except StAR and P450 side-chain cleavage enzyme deficiencies) from the rest of the etiologies leading to PAI, as non-CAH is characterized by elevated ACTH concentrations and low steroidogenic intermediates.

The presence of hyperpigmentation of skin, nail beds, mucous membranes, palmar creases and scars is one of the hallmarks of primary adrenocortical pathology. ACTH and alpha-melanocyte stimulating hormone (α-MSH) are cleavage products of pro-opiomelanocortin (POMC). In patients with low cortisol levels as a consequence of adrenal disorders, POMC synthesis and consequently ACTH and MSH levels rise by negative feedback mechanisms. α-MSH then binds to the melanocortin 1 receptor on melanocyte cells, inducing a switch from the production of the pale skin pigment pheomelanin to eumelanin which is the darker (brown or black) pigment (7).

Clinical presentation may be mild or severe depending on the degree of impairment of enzyme activity and there may be signs, symptoms and laboratory findings of cortisol deficiency, mineralocorticoid deficiency or excess, undervirilization or androgen excess in males and sexual infantilism or virilization in affected females. The main signs and symptoms of cortisol deficiency include anorexia, weight loss, fatigue, myalgia, joint pain, low blood pressure, orthostatic hypotension, hyponatremia, hypoglycemia, lymphocytosis and eosinophilia and in addition direct hyperbilirubinemia and apnea may be present in newborn babies. Mineralocorticoid synthesis and release is under the control of the renin-angiotensin system, rather than ACTH. Therefore, mineralocorticoid deficiency develops only in adrenocortical abnormalities. Mineralocorticoid deficiency causes failure to thrive, abdominal pain, nausea, vomiting, dizziness, low blood pressure, orthostatic hypotension, hyponatremia, salt craving, hyperkalemia, metabolic acidosis, dehydration and hypovolemic shock. Lack of pubic and/or axillary hair and absent/delayed clinical adrenarche in either sex suggests deficiency of adrenal sex steroids.

More than 95% of all cases of CAH are caused by 21-hydroxylase deficiency (21-OHD). 21-OHD is classified into 3 subtypes according to retained enzyme activity and clinical severity: classic salt wasting, classic simple virilizing, and nonclassic CAH (NCCAH; mild or late onset) (6,8). The classic type affects approximately 1 in 16.000 live births. NCCAH is one of the most common autosomal recessive disorders in humans and affects approximately 1 in 1000 individuals (6). The second most common form of CAH, 11β-hydroxylase deficiency (11-OHD), occurs in 1 in 100,000 live births and accounts for approximately 5% of cases (9). Other less common forms of CAH include 3β-hydroxysteroid dehydrogenase type 2 deficiency, 17α-hydroxylase deficiency, POR deficiency, lipoid CAH and cholesterol side-chain cleavage enzyme deficiency. Distinctive clinical and biochemical features and management goals of CAH are presented in Table 2. An expert review on the genetic features of CAH is also available (6).

Advances in steroid assays in recent years, particularly the clinical utility of liquid chromatography/tandem mass spectrometry (LC-MS/MS), have allowed more accurate quantitation of key steroids, simultaneous measurement

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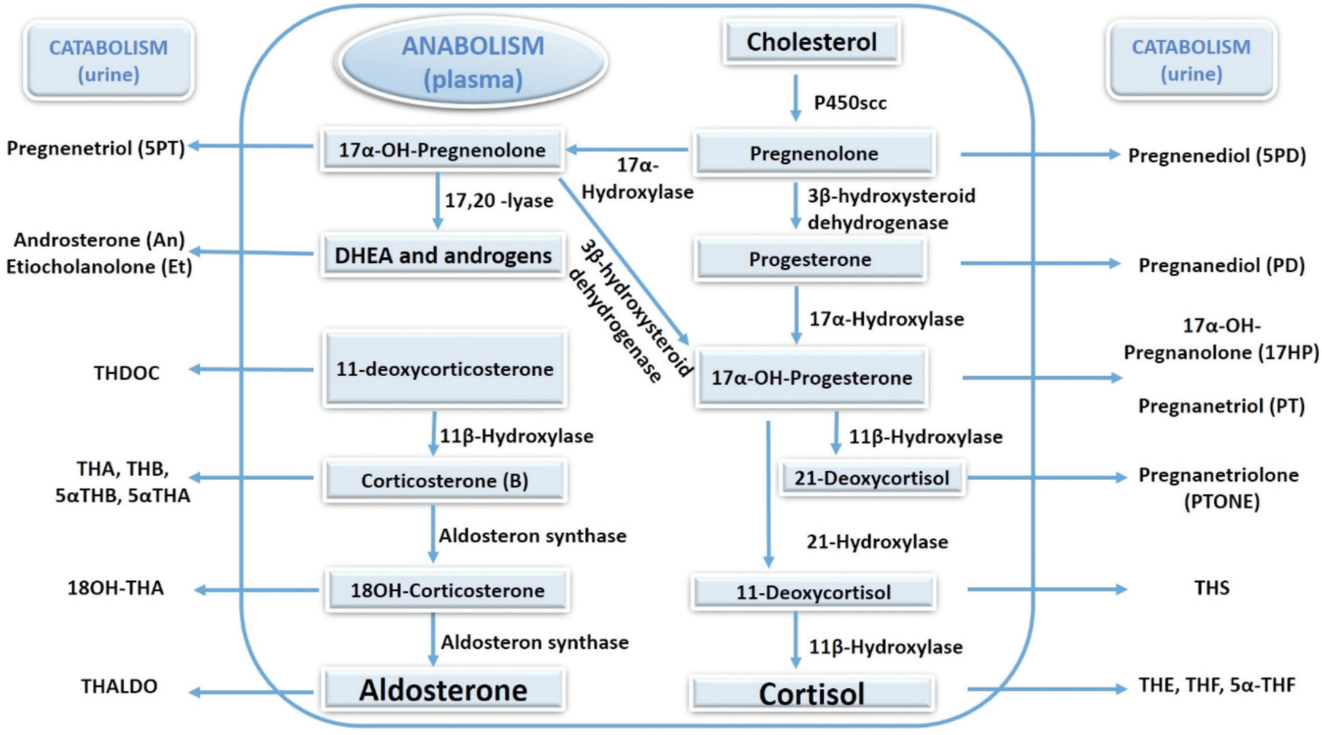

Figure 1. Adrenal steroidogenesis showing the main enzymatic steps of the pathway, intermediate precursors measurable in plasma and their respective catabolic metabolites detectable in the urine

P450scc: P450 side chain cleavage, DHEA: dehydroepiandrosterone, THDOC: tetrahydrodeoxycorticosterone, 18OH-THA: 18OH-tetrahydrodehydrocorticosterone, (5α)THA: (5α)tetrahydrodehydrocorticosterone, (5β)THB: (5β)tetrahydrocorticosterone, THALDO: tetrahydroaldosterone, THS: tetrahydrodeoxycortisol, THE: tetrahydrocortisone, (5α)THF: (5α)tetrahydrocortisol

of multiple steroids from small biological samples and identification of novel steroids in the pathogenesis of adrenal disorders. The best example of this is the emerging evidence of 11-oxygenated 19-carbon (11oxC19) adrenal-derived steroids as clinically important androgens. 11oxC19 steroids are synthesized by the action of cytochrome P450 11β-hydroxylase. Besides the last step of cortisol biosynthesis, cytochrome P450 11β-hydroxylase mediates the conversion of androstenedione and testosterone into their respective 11-oxygenated products, namely 11β-hydroxyandrostenedione (11OHA4) and 11β-hydroxytestosterone (11OHT). These steroids are further converted to small amounts of 11-ketoandrostenedione (11KA4) and 11-ketotestosterone (11KT) respectively, by the action of 11β-hydroxysteroid dehydrogenase, type 2. 11oxC19 steroids are produced almost exclusively from the adrenal gland and they were shown to be three to four times higher in 21OHD patients than in controls. In addition 11KT was found to be more closely associated with poor control in 21OHD than testosterone levels in both males and females. Therefore it has been hypothesized that 11KT is a major adrenal androgen, responsible for suppression of gonadal functions observed in poorly controlled 21OHD (10). Furthermore, 21-deoxycortisol and 11oxC19 steroids showed the closest correlation with adrenal gland size and 11oxC19 steroids were detected at much higher concentrations in CAH patients with testicular adrenal rest tumor (TART) than those without (11). These findings suggest that 11oxC19 steroids may present clinically promising biomarkers in the treatment monitoring and management of CAH.

Adrenal Dysgenesis/Hypoplasia

During the last two decades, high-throughput sequencing approaches proved very effective in reaching a molecular diagnosis for several forms of primary adrenal hypoplasia and adrenal dysgenesis syndromes. The genetic basis for these disorders involves various cellular and physiologic processes, including metabolism, nuclear protein import, oxidative stress defense mechanisms and regulation of cell cycle (12). Two distinct histological patterns of adrenal hypoplasia have been described; the miniature adult and cytomegalic forms. In the miniature adult form, adrenal cortex has normal structural organization whereas in the cytomegalic form of primary adrenal hypoplasia the residual adrenal cortex is structurally disorganized with scattered irregular nodular formations of eosinophilic cells, with the adult permanent zone absent or nearly absent. The

Table 2. Clinical and laboratory findings of different forms of congenital adrenal hyperplasia and treatment goals

Condition	Clinical landmarks	Impaired steroidogenesis	Steroid status	Laboratory findings	Treatment
21α-hydroxylase deficiency	Cortisol deficiency, mineralocorticoid deficiency (salt-wasting crisis), 46,XX DSD, postnatal virilization in both sexes	Adrenal	Glucocorticoids and mineraocorticoids↓, adrenal sex steroids↑	Serum/plasma: Cortisol↓ ACTH↑ serum basal and ACTH-stimulated 17OHP↑ 21-deoxycortisol*↑, 4AS↑ testosterone↑ hyponatremia, hyperkalemia, plasma renin activity↑ Urine: Pregnanetriolone§↑, Pregnanetriol↑, 17αOH-Pregnanolone↑	Glucocorticoid (hydrocortisone), mineralocorticoid and salt replacement, vaginoplasty, cliteroplasty, suppression of hyperandrogenism by glucocorticoids
11β-hydroxylase deficiency	Cortisol deficiency, 46,XX DSD, postnatal virilization in both sexes, hypertension	Adrenal	Glucocorticoids↓, mineralocorticoids and adrenal sex steroids↑	Cortisol↓ ACTH↑ serum basal and ACTH-stimulated 11-deoxycortisol* and deoxycorticoserone↑, 4AS↑, testosterone↑ hypokalemia, plasma renin activity↓ Urine: Tetrahydrodeoxycortisol§↑	Glucocorticoid (hydrocortisone) replacement, vaginoplasty, cliteroplasty, suppression of hyperandrogenism by glucocorticoids
3β-hydroxysteroid dehydrogenase type 2	Cortisol deficiency, Mineralocorticoid deficiency (salt-wasting crisis) 46,XX and 46,XY DSD, pubertal disorders and premature adrenarche in both sexes	Adrenal, gonadal	Glucocorticoids, mineralocorticoids and adrenal sex steroids↓	Cortisol↓ ACTH↑ serum basal and ACTH-stimulated Δ5 steroids (pregnenolone, 17-hydroxypregnenolone*, DHEA)↑, 4AS↓ testosterone↓ hyponatremia, hyperkalemia, plasma renin activity↑ Urine: Pregnenetriol§↑, pregnenediol↑	Glucocorticoid (hydrocortisone), mineralocorticoid and salt replacement, genitoplasty, sex steroid replacement at puberty, suppression of hyperandrogenism by glucocorticoids
17α-hydroxylase / 17,20 lyase deficiency	Cortisol deficiency (excessive deoxycorticosterone masks clinical findings of glucocorticoid deficiency), 46,XY DSD, Absence of pubertal development, hypertension	Adrenal, gonadal	Glucocorticoids and adrenal sex steroids↓, mineralocorticoids ↑	Cortisol↓ ACTH↑ serum basal and ACTH-stimulated corticosterone and 11-deoxycorticosterone*↑, 17α-hydroxylated steroids↓, 4AS↓ testosterone↓ hypokalemia, plasma renin activity↓ Urine: (5α)Tetrahydrodehydrocorticosterone↑, (5β)Tetrahydrocorticosterone↑ Androsterone↓, Etiocholanolone↓	Glucocorticoid (hydrocortisone), replacement, genitoplasty, sex steroid replacement at puberty
Congenital lipoid adrenal hyperplasia (StAR deficiency), P450 side chain cleavage (CYP11A1) deficiency	Cortisol and mineralocorticoid deficiency (salt-wasting crisis), 46,XY DSD, absence of pubertal development and premature ovarian failure in females	Adrenal, gonadal	Glucocorticoids, mineralocorticoids and adrenal sex steroids↓	Cortisol↓ ACTH↑ serum basal and ACTH-stimulated steroids and their precursors are low, hyponatremia, hyperkalemia, plasma renin activity↑, FSH and LH↑, testosterone and estradiol↓	Glucocorticoid (hydrocortisone), mineralocorticoid and salt replacement, genitoplasty, sex steroid replacement at puberty
P450 oxidoreductase deficiency	Cortisol deficiency, 46,XX and 46,XY DSD, Antley-Bixler syndrome, maternal virilization	Adrenal, gonadal		Cortisol↓ ACTH↑ pregnenolone↑, progesterone↑, prenatal androgens↑, androgen and estrogens at puberty↓ Urine: Pregnanetriol↑, 17αOH-pregnanolone↑, androsterone↓, etiocholanolone↓	Glucocorticoid (hydrocortisone) mineralocorticoid and salt replacement, genitoplasty, sex steroid replacement at puberty

*Best diagnostic biochemical marker in serum, §Best diagnostic biochemical marker in urine
ACTH: adrenocorticotropin hormone, StAR: steroidogenic acute regulatory protein, LH: Luteinizing hormone, FSH: follicle stimulating hormone, DHEA: dehydroepiandrosterone

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miniature adult form is generally sporadic or inherited in an autosomal recessive manner while the cytomegalic form is generally considered to be X-linked, but there may be one or more autosomal genes associated with this phenotype (12). Regardless of underlying genetic etiology, conditions with adrenal hypoplasia/dysplasia are associated with deficiency of all adrenocortical hormones (aldosterone, cortisol, androgens). Most common is DAX1 deficiency which is due to genetic defects in *NR0B1*, located on chromosome Xp21.2. DAX1 defects have been detected in two thirds of males with PAI of unknown etiology by clinical or biochemical phenotype (13). Therefore all male patients with a history of non-CAH PAI should be screened for DAX1 deficiency, especially those with infertility, delayed/absent puberty or adrenal insufficiency in males from the maternal family. Adrenal insufficiency shows a bimodal distribution pattern of age at presentation ie either around newborn period or after 1 year of age. However late-onset DAX1 deficiency cases are also being increasingly reported from adult clinics (3,14). Patients with DAX1 deficiency present with variable phenotypes. Typically, they develop severe primary adrenal failure with salt-wasting. The hypogonadotropic hypogonadism may manifest as delayed puberty, impaired spermatogenesis or infertility which is explained by the expression of *NR0B1* in the hypothalamus and the anterior pituitary, besides the adrenal glands and the gonads. Therefore, long-term focus on puberty and fertility is needed in affected individuals. Ambiguous genitalia is not a feature of DAX1 deficiency. However micropenis and or cryptorchidism may be present. Patients with precocious puberty have also been reported (15,16). Although this is an X-linked condition, females carrying homozygous or heterozygous mutations have also been reported to express phenotypic features of adrenal hypoplasia congenital due to non-random X inactivation (17,18). Genetic counselling can help to identify family members at risk of adrenal insufficiency and female carriers.

The SF1 protein, encoded by the nuclear receptor subfamily 5, group A, member 1 (*NR5A1*) gene, is expressed in the adrenal gland, gonads, hypothalamus and anterior pituitary. SF1 has a crucial role in adrenal gland, gonads and spleen development in both sexes. Besides, SF1 is involved in the regulation of energy balance and glucose homeostasis in the central nervous system (19). SF1 deficiency develops as a result of pathogenic mutations in *NR5A1* gene in both heterozygous or homozygous inheritance. In contrast to DAX1-associated diseases, SF-1 deficiency only rarely causes adrenal insufficiency, but generally in combination with testicular dysgenesis. Isolated adrenal failure has rarely been reported (20). However, long-term follow-up for adrenal function is important for those patients with *NR5A1* mutations. Phenotypic features in 46,XY individuals with *NR5A1* mutations include different forms of disorders of sex differentiation (DSD) ranging from hypospadias to complete female phenotype or late-onset impaired spermatogenesis and infertility. *NR5A1* gene defects should also be considered in 46,XY DSD cases with normal testosterone concentrations, similar to androgen receptor (*AR*) mutations or mild 5-α reductase, or mild 17-ketosteroid reductase deficiencies. Mutations in *NR5A1* were found in 46,XX females with isolated/premature ovarian insufficiency (14). 46,XX testicular/ovotesticular DSD is also described in one case (21,22). Poly/asplenia can be seen in both sexes (23).

The common feature of syndromes associated with adrenal hypoplasia is the severe impairment of growth and tissue development and particularly with a prenatal onset. These disorders specifically impair the machinery involved in cell division and cell cycling. The author suggests evaluation of adrenal function in any patient with severe, prenatal-onset growth retardation and with syndromic features, especially with cerebral and finger malformations (Table 1).

Here, two specific examples of syndromic adrenal hypoplasia are given.

IMAGe syndrome is a recently described, syndromic adrenal hypoplasia syndrome associated with severe growth failure. This syndrome develops as a result of impaired expression of a cell cycle regulator protein, cyclin dependent kinase inhibitor 1C (CDKN1C). CDKN1C, encoded by the *CDKN1C* gene, is a negative regulator of cell proliferation maintaining the cell at the non-proliferative state throughout life. The loss-of-function mutations, located at the CDK-binding domain of the *CDKN1C* gene, are associated with Beckwith-Wiedemann syndrome. Recently, gain-of-function mutations in the PCNA domain of *CDKN1C* have been have been described in association with various growth-retarded syndromes including IMAGe syndrome and Russell Silver syndrome as well as a novel undergrowth syndrome that additionally exhibits early adulthood onset diabetes (24). *De novo* heterozygous *CDKN1C* mutations or imprinted mode of inheritance with maternal transmission of *CDKN1C* mutations were reported. Early recognition of metaphyseal dysplasia accompanying early-onset, severe adrenal insufficiency is crucial for the diagnosis IMAGe syndrome. Delayed endochondral ossification, osteopenia, hypercalcemia, and/or hypercalciuria of variable degree are among the early findings. Dysmorphic craniofacial features including prominent forehead, low-set ears, short nose, flat nasal bridge, rhizomelic shortening and genital abnormalities in males are other associated features.

Another severe growth-restricting pathology associated with adrenal hypoplasia has recently been described in patients due to gain-of-function mutations in the *SAMD9* gene. Growth and survival is so impaired in this genetic disorder that affected individuals develop tissue adaptation by progressive loss of mutated *SAMD9* in chromosomal structure. This modification is achieved through the development of monosomy 7 (-7), deletions of 7q (7q-), and secondary somatic loss-of-function (nonsense and frameshift) mutations in *SAMD9* to rescue the growth-restricting effects of mutant SAMD9 proteins in bone marrow and to increase the length of survival (25). So the use of advanced diagnostic and molecular technologies has helped to define novel mechanisms in human development beyond genetic defects in adrenal development and adrenal steroidogenesis.

Affected individuals with heterozygous gain-of-function mutation in *SAMD9* present with MIRAGE syndrome, which is an acronym of myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, and enteropathy (26).

Adrenocorticotropin Hormone Resistance

Mutations in *MC2R* (encoding the ACTH receptor protein, MC2R) and *MRAP* (encoding MC2R accessory protein) are well described causes of inherited disorders of ACTH binding and signaling, namely FGD type 1 (FGD1) and type 2 (FGD2). FGD is characterized by cortisol deficiency together with a preserved renin-aldosterone axis. Children typically present with hypoglycemia or hyperpigmentation in early infancy or in childhood. Some associated phenotypical features may also be present (Table 1). Children with FGD do not typically have salt-loss. However, transient hyponatremia has been reported in several children with severe *MC2R* defects, sometimes leading to a misdiagnosis of adrenal hypoplasia (3). Plasma ACTH often remains markedly raised despite normal or even supranormal glucocorticoid treatment. Therefore, affected patients remain hyperpigmented. So the clinical aim of glucocorticoid replacement strategies should not be to suppress ACTH or normalization of hyperpigmentation but should rather target normal water and electrolyte balance and a normal physical growth rate.

Mitochondria and Adrenal Gland

Recent advances in molecular studies and application of genome-wide, next-generation sequencing approaches revealed the importance of mitochondrial function for endocrine health and steroid hormone biosynthesis. All steroid hormones are synthesized within mitochondria by tissue-specific steroidogenic enzymes (Figure 2). Mitochondrial dysfunction may affect the capacity for adrenocortical hormone production by impaired mitochondrial ATP production, oxidative stress and/or accelerated apoptosis (27). In particular some of the latest findings have expanded the spectrum of pathogenetic mechanisms causing adrenal disease and imply that the adrenal is highly vulnerable to oxidative stresses (Figure 2) (28,29).

Molecular defects in both mitochondrial and nuclear genomes have been associated with mitochondrial dysfunction (Table 1). Clinicians should have a high level of suspicion for the possibility of an underlying mitochondrial disease in patients with adrenal insufficiency associated with sensorineural hearing loss, lactic acidosis and accompanying endocrine abnormalities (diabetes, hypoparathyroidism, hypogonadism, hypothyroidism) and multisystemic diseases (epilepsy, stroke, encephalopathy, cranial abnormalities, cardiac conduction defects, neuropathy, retinopathy).

Sphingolipids and Adrenal Gland

The essential role of sphingolipid metabolism has recently emerged in adrenal disease. Congenital sphingosine1phosphate (S1P) lyase deficiency due to biallelic mutations in the *SGPL1* gene has been described, in association with PAI and steroid-resistant nephrotic syndrome (30,31,32). S1P lyase is the enzyme responsible for irreversible S1P degradation which is the final step in sphingolipid breakdown. Inhibition of S1P lyase activity will lead to accumulation of bioactive signaling molecules upstream of the pathway including S1P and ceramides (Cer). We have recently demonstrated that accumulation of S1P, Cer and potentially other upstream components of the sphingolipid pathway, due to congenital S1P lyase deficiency, leads to a multisystemic disorder including PAI, nephrotic syndrome and ichthyosis, primary hypothyroidism, cryptorchidism, lymphopenia and neurological anomalies.

Establishing a specific genetic diagnosis of PAI is extremely valuable for identifying presymptomatic children who could benefit from treatment before the onset of potentially life-threatening symptoms and for counseling family members appropriately about the risk of passing the condition on to their children. Knowing the genetic etiology can also help to modify treatments, such as the need for long-term mineralocorticoid replacement, and can predict potential co-morbidities, such as impaired puberty or fertility and neurological dysfunction. An etiological approach in children with Inherited Primary Adrenal Insufficiency is suggested in Figure 3.

Treatment

Replacement of glucocorticoids and mineralocorticoids, particularly by hydrocortisone and fludrocortisone is

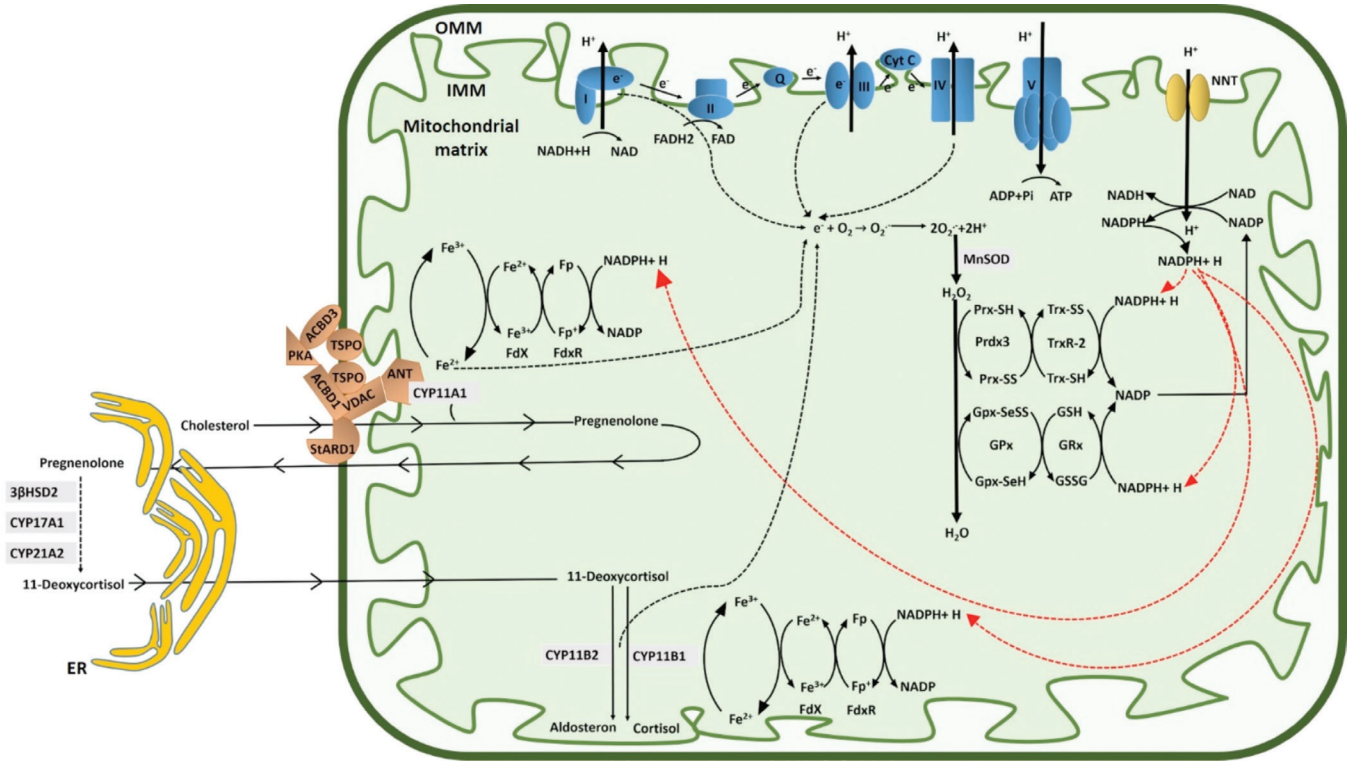

Figure 2. Mitochondrial machinery involved in the regulation of steroidogenesis. Access of cholesterol to the mitochondria is regulated by the steroidogenic acute regulatory protein, (StAR), serving as the acute regulator of steroidogenesis. StAR action requires interaction with the transduceosome complex that is composed of a group of proteins (translocator protein, voltage dependent anion channel 1, ACBD3, adenine nucleotide transporter, protein kinase A) at the inner mitochondrial membrane in the process of transporting cholesterol molecules directly to the cholesterol side chain cleavage enzyme, P450scc (CYP11A1) to initiate steroidogenesis. CYP11A1 is the enzymatic rate-limiting step in steroidogenesis which determines cellular steroidogenic capacity. CYP11A1, CYP11B1 and CYP11B2 are the main mitochondrial cytochrome P450 enzymes involved in steroidogenesis. Four complexes of the electron transport chain (indicated in blue) transfer electrons to generate energy required for various cellular processes including steroid biosynthesis. Nicotinamide nucleotide transhydrogenase (NNT), is an integral protein of the inner mitochondrial membrane. This enzyme uses energy from the mitochondrial proton gradient to produce high concentrations of nicotinamide adenine dinucleotide phosphate (NADPH). NADPH is the electron supplier for two electron-transfer intermediates, ferredoxin reductase and ferredoxin which are required for mitochondrial P450 enzymes to produce steroid hormones. NADPH is also used by mitochondrial antioxidant defence machinery, comprising glutathione peroxidase (Gpx) and the peroxiredoxin-thioredoxin systems, which are responsible for the inactivation of reactive oxygen species derived from the leakage of electrons from electron transport chain during energy generation procedures. Genetic defects in many components of this machinery (including StAR, CYP11A1, CYP11B1, NNT, TXNRD2, GPX1, PRDX3) have been described in patients with primary adrenal insufficiency

TSPO: translocator protein, VDAC: voltage dependent anion channel, ANT: adenine nucleotide transporter, PKA: protein kinase A; FdXR: ferredoxin reductase, FdX: ferredoxin, Gpx: glutathione peroxidase, NADPH: nicotinamide adenine dinucleotide phosphate, NNT: Nicotinamide nucleotide transhydrogenase, StAR: steroidogenic acute regulatory protein, Prdx-Trx: peroxiredoxin-thioredoxin

the mainstay of treatment in adrenal insufficiency. Intravenous fluids and salt replacement should be added to the treatment in stressful conditions and adrenal crisis. Principal treatment goals include maintaining a physiologic water and electrolyte homeostasis together with attainment of normal physical and pubertal growth. CAH management should also target reduction of androgen exposure. Additionally, optimization of hydrocortisone treatment is critical to mimic the physiological circadian rhythm of cortisol secretion and to avoid excessive glucocorticoid exposure which is associated with poor long-term health outcomes, including growth suppression, obesity, metabolic syndrome, diabetes and osteoporosis (33). These challenges have led to the development of new glucocorticoid formulations and some adjuvant treatments (34). In recent years, investigators have developed two modified-release, oral, glucocorticoid preparations. The first is a dual-release hydrocortisone with an extended-release core surrounded by an immediate-release coating (Plenadren; ViroPharma, Maidenhead, UK), which was developed for once-daily, first-morning administration in patients with PAI. However, it is unable to deliver a sufficient early morning cortisol rise and

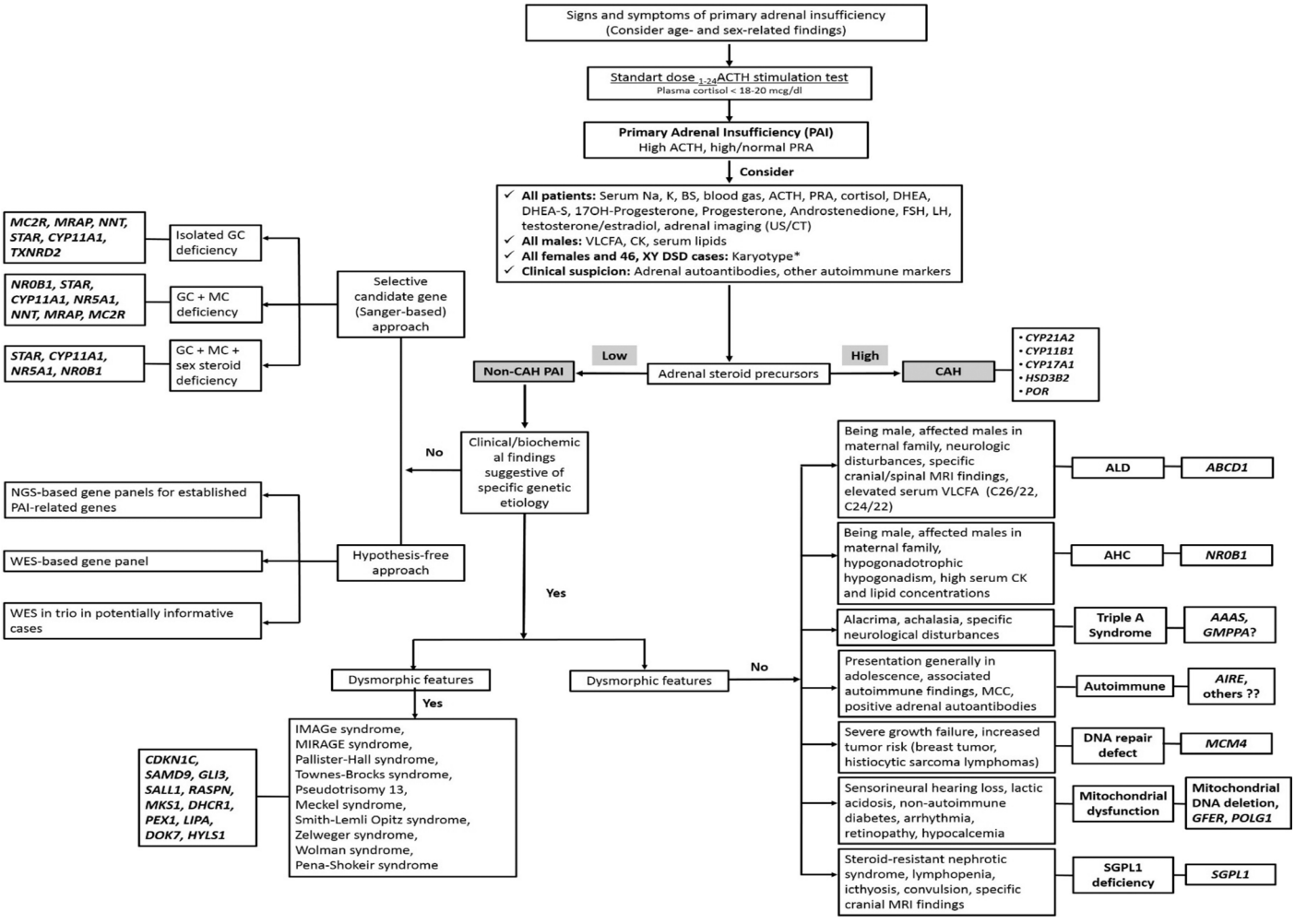

Figure 3. A proposed diagnostic work up algorithm for targetted genetic testing to determine the etiologic diagnosis in inherited primary adrenal failure in children

*Karyotype can be excluded in female phenotype patients whenever pelvic US confirms the presence of normal ovaries and Mullerian structures. Assessment of karyotype-matched normal external and internal genitalia and gonads is crucial for deciding about gonadal sex steroid production

ACTH: adrenocorticotropin, PRA: plasma renin activity, Na: sodium, K: potassium, BS: blood sugar, DHEA: dehydroepiandrosterone, FSH: follicle-stimulating hormone, LH: luteinizing hormone, VLCFA: very-long-chain fatty acids, CK: creatinine kinase, US: ultrasound, CT: computerized tomography, CAH: congenital adrenal hyperplasia, GC: glucocorticoid, MC: mineralocorticoid, MRI: magnetic resonance imaging, ALD: adrenoleukodystrophy, AHC: adrenal hypoplasia congenital, MCC: mucocutaneous candidiasis, NGS: next generation sequencing, WES: whole exome sequencing, SGPL1: sphingosine-1-phosphate lyase

to suppress ACTH and adrenal androgens in the morning by once-daily dosing. Plenadren failed to achieve physiologic cortisol replacement in a small case series of children with non-CAH primary adrenal failure and secondary adrenal insufficiency (35,36,37). Plenadren is not yet licensed for use in the management of adrenal insufficiency in children, but is available for use in adult patients with a good safety profile (38). The second formulation is a delayed and sustained release, multiparticulate hydrocortisone, Chronocort® (Diurnal, UK). Chronocort given at morning and night doses provides release of hydrocortisone in the early hours of the morning, replicating a physiological cortisol secretion pattern. It also appears to achieve better control of excessive androgen synthesis produced via classical and alternative pathways through attenuation of androstenedione and 17OH-progesteron (39). There is an ongoing phase III study to evaluate long-term effects of Chronocort treatment. This drug is also not licenced for use in children. There are a few recent trials to evaluate the bioavailability and absorption of modified hydrocortisone formulations, such as granules or sprinkles, for young children (Infacort®, Diurnal Ltd) (40). Continuous subcutaneous hydrocortisone infusion (CSHI) via a pump, similar to an insulin pump, is superior in achieving a better cortisol secretion profile and lowering ACTH concentrations in non-CAH PAI and in lowering serum androgens in CAH (41,42). However, certain issues limit the

use of CSHI including high cost, complexity of device usage, the need for patient/parent education, the potential for local irritation and the potential for uninterrupted equipment wear and malfunction which would be particularly risky in patients with complete glucocorticoid deficiency. A recent meta-analysis demonstrated that extended-/dual-release and CSHI forms of glucocorticoid treatments are associated with higher life quality scores over the short-term (43).

Non-glucocorticoid adjuvant pharmacologic treatments for adrenal failure mainly target control of hyperandrogenism in CAH (34). Among them, abiraterone may be a promising alternative therapy that decreases the need for supraphysiologic exogenous glucocorticoids. Abiraretone is a potent inhibitor of CYP17A1, required for the synthesis of gonadal and adrenal androgens. Combined use of abiraterone with glucocorticoids can effectively lower androstenedione and testosterone metabolites in adult women with 21OHD without any potential side effects including hypertension and hypokalemia. However, it does not lower ACTH and inhibits gonadal sex-steroid secretion which limits its use in males with TART and for patients who desire fertility (44). A CRH receptor-1 antagonist was used in a Phase 1 trial of eight CAH women at a single dose which showed a 40% reduction in morning ACTH rise to control hyperandrogenism (45).

Conclusion

PAI is a relatively rare but potentially lethal clinical condition in children. Early recognition of adrenal insufficiency can be difficult, although treatment is usually successful once it is initiated and, in most cases, lifelong treatment is necessary. Monogenic conditions, particularly CAH, account for most cases of PAI in childhood. Application of omics-based approaches by LC combined with MS significantly facilitated the recognition of biochemical markers of various steroidogenic enzyme deficiencies. In particular, targeted LC-MS/MS steroid panels, besides being very well suited for the routine laboratory setting, have proven extremely useful in diagnosing CAH subtypes and guiding treatment. However, non-CAH PAI often remains without a definite cause in a substantial number of cases. Detailed clinical phenotyping of such cases is critically important for diagnostic workflow but genotyping is equally important, confirming the diagnosis or carrier state, providing prognostic information on disease severity and is essential for genetic counseling.

Adrenal insufficiency is associated with a reduced quality of life that may be caused by non-physiological glucocorticoid replacement. In recent years, a substantial amount of progress has been made in optimizing glucocorticoid delivery systems, as well as by exploring non-glucocorticoid therapeutic strategies in CAH. However, there is still a long way to go in developing disease-specific and personalized treatments for children with PAI.

Ethics

Peer-review: Internally peer-reviewed.

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