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Review

Hormone resistance in children: what primary care physicians need to know

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Abstract. Hormone resistance is defined as a reduced or absence of target tissues responsiveness to a hormone, where the presentation is related to either a relative lack or excess of hormones. Various disorders of hormone resistance were encountered including, Laron syndrome, nephrogenic diabetes insipidus, thyroid hormone resistance syndrome, pseudohypoparathyroidism, insulin resistance, familial glucocorticoid deficiency, pseudohypoaldosteronism, X linked hypophosphatemic rickets and androgen insensitivity syndrome. The article gives a summary that presents, in concentrated form, what the primary care physicians need to know about recognition, clinical presentation, diagnosis, and management of various hormone resistance in children.

Key words: hormone resistance, laron syndrome, pseudohypoparathyroidism, insulin resistance, thyroid hormone resistance

Introduction

Hormone resistance is an endocrinal disease caused by a reduced or absent end-organ responsiveness to a biologically active hormone, which may occur at several levels: pre-receptor, receptor, or post-receptor (1). This condition was first described in 1942 and, since then, resistance to the effect of many hormones has been described. The characteristic feature of hormone resistance is the presence of a normal or elevated level of the hormone in the circulation that arises due to loss of regulatory feedback control between the target tissue and the hormone (2). In the past, the diagnosis of most hormone resistance syndromes can be made by upon measurements of circulating hormone levels at various points in a given endocrine axis. Currently, although such measurements are still very important for diagnostic and therapeutic purposes, the molecular genetic study is used to provide many insights into the structure and function of receptors and permit genetic counseling within families (3). Although treatment of hormone resistance is straightforward on most occasions, it is challenging in others (1). In this review, the authors spotlighted the clinical presentation, investigation, and up-to-date management of various resistance syndrome in children.

Laron syndrome

Laron syndrome (LS) or growth hormone insensitivity is an autosomal recessive disease characterized by a lack of insulin-like growth factor 1(IGF-1) resulting from growth hormone receptor (GHR) mutations (4). In addition to short stature, other criteria of LS are summarized in table 1 (4,5). The metabolic abnormalities associated with LS including hyper-lipidemia and recurrent hypoglycemia, especially during infancy (6). The average height attained by subjects with LS are approximately 4-4.5 feet in women/men respectively,

if untreated (7). The laboratory diagnosis of LS include extremely elevated serum human growth hormone(hGH) concentrations despite low serum IGF-1 levels with failure of IGF-1 to increase in response to exogenous hGH (IGF-1 stimulation test) (4). The diagnosis can be confirmed by the molecular genetic study to detect the accurate defect in the GH receptor gene(8). Recombinant human IGF-1 (rh IGF-1) has been used in the treatment of children with LS by subcutaneous administration in a dose of 75 mg/kg/day (9). Prolonged treatment improves the linear growth, growth of hands, feet, chin, and nose as well as the onset of puberty. Side effects include electrolyte disturbance and calciuria(5).

Nephrogenic diabetes insipidus

Nephrogenic diabetes insipidus (NDI) is a polyuric condition that results from partial or complete resistance of the late distal tubules and collecting ducts to the actions of arginine vasopressin (AVP). The causes of NDI are listed in table 2 (10,11). Most patients with congenital NDI present with failure to thrive during the first few months of life, whereas those with acquired NDI typically present later in life with polyuria and or polydipsia (10,11).Laboratory evaluation must also include serum osmolality and urine osmolality. NDI is associated with urine that is inappropriately dilute with a urine osmolality less than 300 mOsm/kg in the setting of a serum osmolality greater than 300 mOsm/kg without change in urine osmolality after administration of exogenous vasopressin(12). Plasma vasopressin and copeptin levels may be useful in distinguishing NDI from central diabetes insipidus (CDI) , with higher levels indicating NDI and lower levels in CDI(13). The diagnosis of hereditary NDI is usually established by molecular genetic testing (11). Management of NDI consists of dietary restriction of proteins and sodium, amiloride diuretics, and prostaglandin inhibitors are currently the mainstay of NDI treatment (14).

Thyroid hormone resistance syndrome

Thyroid hormone resistance syndrome (THRS) is a rare autosomal dominant or recessive disorder that occurs in either familial and sporadic form(15). The incidence of THRS is approximately 1:50,000, and THRS cases are caused by genetic mutations in the thyroid hormone receptor β (THRβ) gene(16). Variability in the responsiveness of tissues to thyroid hormones explains the different clinical presentations

Table 1. Clinical creiteria symptoms of Laron syndrome

- Short stature (height < -3 SD score).
- Obesity.
- Small head.
- Prominent forehead, depressed nasal bridge and saddle nose.
- Sparse growth of hair.
- Crowded, defect teeth.
- High pitched voice.
- Acromicria (small chin, hands, feet)
- Hypogonadism.
- Delayed bone age.
- Slow motor development.

Table 2. Causes of NDI in children

Congenital	Acquired
• X-linked NDI- Xq28 encoding AVPR2 (arginine vasopressinreceptor 2). • Autosomal recessive NDI- Ch12q13 encoding AQP2.	• Electrolyte abnormalities: hypokalemia, hypercalcemia, hypercalciuria. • Renal parenchyma disorders, obstructive uropathy. • Systemic disorders: sickle cell disease and trait ,sarcoidosis and amyloidosis. • Drugs : aminoglycoside, methicillin, rifampin furosemide, colchicine and vinblastine.

of THRS (hyper- or hypothyroidism)(17).In addition to the goiter, the presenting features in children with THRS were enumerated in table 3 (18). In THRS, thyroid function tests show increased levels of both total and free T3 and T4 in the presence of unsuppressed TSH, which may be either normal or slightly increased(17). The distinction between THRS and TSH-producing pituitary tumor may be difficult as there are no significant differences in FT4, FT3 ,and TSH concentrations in both the conditions. Pituitary imaging may help to differentiate the two conditions (19). The treatment decision depends on the individual characteristics of each patient (15). Patients with THRS in a compensated euthyroid state do not need treatment. Patients with hypothyroid and hyperthyroid symptoms may require treatment with thyroid hormone and with drugs such as beta- blockers, antithyroid drugs, and thyroid hormone analogue (18).

Pseudohypoparathyroidism

Pseudohypoparathyroidism (PHP) is a rare inherited disorder characterized by target organ resistance to parathyroid hormone (PTH) (20). The syndrome mimics hypoparathyroidism with patients presented with hypocalcemia and hyperphosphatemia, however, the parathyroid hormone is inappropriately high (21). The clinical manifestations of the classical phenotype of Type 1a PHP (Albright hereditary osteodystrophy) are listed in table 4 (22).

Table 3. Clinical features of thyroid hormone resistance

Goitre
Emotional disturbances
Delayed bone age
Attention deficit hyperactivity disorder
Tachycardia
Hyperkinetic behaviour
Low body mass index
Learning disability
Short stature
Hearing loss (sensorineural)
Mental retardation

Type 1b PHP patients lack the physical appearance of Type 1a, but have similar biochemical abnormalities (23). The diagnosis of PHP is based on clinical characteristics and labaratory findings, but, whenever possible, should be confirmed by molecular genetic testing(20).The overall goals in the treatment of PHP are to maintain normal calcium, normal phosphorus, avoid hypercalciuria, and lower PTH levels to normal if possible. PHP should be treated with activated forms of vitamin D, with or without calcium supplementation(20,21).

Familial Glucocorticoid Deficiency

Familial Glucocorticoid Deficiency **(**FGD), also known as hereditary unresponsiveness to ACTH, or isolated glucocorticoid deficiency, is a rare autosomal recessive disorder characterized by severe cortisol deficiency, high plasma ACTH levels, and a well-preserved renin–angiotensin–aldosterone axis(24). FGD is caused by a mutation in the gene for ACTH receptor (melanocortin 2 receptor, MC2R) and melanocortin 2 receptor accessory protein (MRAP) (25). This disorder affects both genders equally and the age of presentation varies from birth to 9 years, with ~50% of cases presenting during the first year of life(26). The presenting symptoms are attributed to glucocorticoid deficiency which is mainly , hypoglycemia , sometimes manifesting as convulsions. Additional features of FGD are reported in table 5 (27).The typical biochemical results in FGD are a combination of low cortisol levels, extremely high plasma ACTH levels

Table 4. Clinical manifestations of Pseudohypoparathyroidism

– Brachydactyly (shortening of fourth and/or fifth metacarpals)
– Early -onset obesity
– Round face
– Intellectual disabilities
– Ectopic ossifications (either clinically evident or at X-ray)
– Reduced IQ
– Acute or chronic hypocalcemia: nervous hyperexcitability with paresthesia, cramps, tetany, hyperreflexia

Table 5. Clinical criteria of familial glucocorticoid deficiency

Presentation in early childhood(50% prior to the age of one year)
Repeated hypoglycemia (neonatal and older)
Lethargy, failure to thrive, collapse, and coma
Recurrent infections
Hyperpigmentation of skin
± Tall stature
Unexplained neonatal deaths in the family
Presence of another affected family member
± Consanguinity

, with no disturbance of electrolyte balance(28). The diagnosis can be confirmed by the molecular genetic study (25). The treatment of FGD is simple in that only glucocorticoid replacement with oral hydrocortisone is required. As with any patient taking glucocorticoids, the dose needs to be increased in times of stress or infections (27).

Pseudohypoaldosteronism

Pseudohypoaldosteronism (PHA) is an autosomal recessive a heterogeneous group of disorders that results from renal tubular resistance to the action of aldosterone, and levels of aldosterone are actually elevated, due to a lack of feedback inhibition(29). This condition mimics hypoaldosteronism and characterized by hypertension, hyperkalemia due to impaired potassium excretion, metabolic acidosis due to decreased urinary H^+ excretion, increased plasma renin activity , and normal both renal function and glomerular filtration rate(30). PHA further sub-classified into PHA type I (PHA-I), which is the classic form, and PHA type II (PHA-II), which is also referred to as Gordon syndrome which is an autosomal dominant disorder characterized by salt-dependent hypertension, hyperkalemia, and metabolic acidosis associated with low plasma renin activity and hyperchloremia (31).Treatment of severe forms of PHA1 requires relatively large amounts of sodium chloride. In contrast, Gordon's syndrome requires salt restriction and the use of thiazide diuretics to block sodium chloride reabsorption and normalize blood pressure and potassium level (32).

Insulin resistance

Insulin resistance (IR) is the most common hormone resistance encountered in pediatric practice (33). IR is mainly caused by obesity ,however, other causes include genetic diseases, the prolonged use of corticosteroids and growth hormone therapy, moreover, puberty is considered as a physiological cause of IR (33).The adverse effects of IR are primarily due to hyperinsulinemia which is the main feature of IR (34). Hyperinsulinemia is an important risk factor for the development of type 2 diabetes (T2D), being one of the two elements involved in the pathogenesis of T2D, together with β-cell dysfunction(35).Moreover, IR is strongly associated with hypertriglyceridemia , low plasma HDL-cholesterol , hypertension, high C-reactive protein levels, and considered a reliable marker in the prediction of cardiovascular risk (34). The gold standard for the diagnosis of IR is the hyperinsulinemic-euglycemic clamp; however the intravenous glucose tolerance test or the insulin tolerance test are more frequently used because they are easier to perform(36). The treatment of IR in children consists of lifestyle modifications, including diet control and increased physical activity. A pharmacologic intervention include weight loss drugs such as sibutramine and orlistat which proved to increase insulin sensitivity (37).

X Linked Hypophosphatemic Rickets

X Linked Hypophosphatemic Rickets (XLH) is inherited in an X-linked dominant disorder, with an incidence of around 1:20,000 (38).It is caused by a mutation in the PHEX gene which is expressed in osteocytes of bones and odontoblasts of teeth, resulting in excessive expression of the phosphaturic factor fibroblast growth factor 23 (FGF23) which impair reabsorption and increased excretion of phosphorus from renal tubules leading to hypophosphatemia (39). This disease was thought to be an inherent defect in the kidney, but when a patient with XLH underwent renal transplantation, the patient's biochemical abnormalities did not improve after transplantation, suggesting that the main defect was in a circulating factor (40). The clinical features of XLH usually present before the

age of 2 years and are similar to the presentation of nutritional rickets with delayed walking ,leg deformities in the form of bow legs or knock knees and disproportionate short stature (41).Additionally delayed dentition; dental abscesses; deafness; craniosynostosis and calcification of entheses may be associated with XLH(41). The disease may be misdiagnosed for vitamin D deficiency, but biochemical abnormalities and, lack of response to vitamin D treatment usually allow the diagnosis (39). The serum biochemical abnormalities including hypophosphatemia, phosphaturia , elevated alkaline phosphatase with normal calcium, PTH, and 25-hydroxyvitamin D(42). Bone radiographs show that growth plates of long bones have a cupped appearance, with increased thickness and irregularities (43).Standard treatment is based on oral phosphate salts supplementation , calcitriol, growth hormone, and anti-calciurics to promote bone growth and diminish mineral loss associated with XLH (41). Burosumab was licensed by FDA in 2018 as the first drug attacking the underlying cause for XLH (44). It is a monoclonal IgG1 antibody that binds excess FGF23 and normalizes phosphorus levels, improve bone mineralization in children (44).

Androgen insensitivity syndrome

Androgen insensitivity syndrome (AIS) formerly known as testicular feminization is a rare X-linked recessive androgen receptor (AR) disorder resulting in a failure of normal virilization of the external genitalia in chromosomally male individuals (45).The individual's AIS has 46XY karyotypeand resistance to the actions of androgens (46). This failure of virilization can be either complete androgen insensitivity syndrome (CAIS) or partial androgen insensitivity syndrome (PAIS), depending on the amount of residual receptor function (45). Most cases of CAIS are identified in the newborn period by the presence of inguinal masses, which later are identified as testes during surgery (47),Some cases are first presented in the adolescence period for evaluation of primary amenorrhea(45). The clinical features of PAIS include ambiguous genitalia ,microphalus , hypospadias ,bifid scrotum and undescended testes [46]. As the testes produce anti-müllerian hormone/factor (AMH) in normal amount , affected individuals do not have fallopian tubes, a uterus, or a proximal vagina(47).A karyotype is mandatory to differentiate an under-- virilized male from an over-virilized female (45).Moreover , the presence of a Y chromosome can be confirmed by fluorescent in situ hybridization (FISH) probes. Mutation analysis of the androgen receptor gene is currently available (48). Management for a patient AIS has 2 arms : hormone replacement therapy and psychological support (47).Because the risk of malignancy is very low in prepubertal patients with CAIS, gonadectomy may be delayed until puberty is complete, allowing it to progress naturally; however, close follow-up of the patient is required(45).

Conclusion

Insulin resistance remains the most common form of hormone resistance in pediatric practice. Although the other forms of hormone resistance that were listed in this article are relatively uncommon, it is important for primary care physicians to be aware of these conditions and their clinical presentation and up-to-date management , due to their high burden on patients' lives and the health care system.

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