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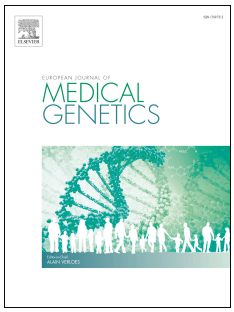

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Pediatric endocrinology through syndromes

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Abstract

In everyday practice, a pediatric endocrinologist will face a variety of different endocrine issues (such as short or tall stature, dysthyroidism, abnormal pubertal timing or impaired glucose metabolism), which relevantly contribute to the global care of a number of syndromic conditions. On the other hand, the presence of endocrine features may assist in the diagnostic process, leading to final diagnosis of a syndromic disorder. The intention of this review is to provide a referenced overview of different genetic syndromes characterized by endocrine features, and to present a possible classification, based on whether the endocrinopathy or the syndrome is typically recognized first. Thus, the first part of the manuscript deals with the most common syndromes associated with endocrine dysfunctions, while the second part describes the conditions by which a syndrome is most frequently diagnosed after an endocrine finding. The aim is to provide a practical overview of the assessment of syndromic patients, so that they can be recognized and managed in an integrated, multidisciplinary fashion.

Keywords

syndrome; stature; puberty; thyroid; diabetes.

Main text

A syndrome is the association of clinically identifiable signs and symptoms, phenomena or characteristics that habitually occur jointly, so that when one or more features are present the physician is alerted to the possible occurrence of the others (indeed, the term derives from the Greek συνδρομή [*sundromē*], composed by the suffix σύν [*syn*], "along with", "together", and the word δρόμος [*dromos*], "course").

In everyday practice, a pediatric endocrinologist will encounter several syndromes which include endocrine features contributing to the devising of global care strategies for patients who have been already diagnosed with a specific syndrome. On the other hand, the presence of specific endocrine issues may be an identifying marker leading to the overall diagnosis of a syndrome. While for some syndromes the connection with endocrine features is well known and easy to detect in common practice, in others the connection may be unfamiliar, hidden and difficult to detect.

In this review we provide an overview and some examples of strong two-way links between pediatric endocrinology and syndromes, as a tool for clinical practice. In the first part we discuss the most common syndromes and the associated endocrine dysfunctions which should be sought (Figure1), while Table 1 contains a more extensive list of syndromes and their relative endocrine findings. Conversely, in the second part, we provide a series of examples of conditions in which a syndrome is frequently diagnosed in a child brought to medical attention for an endocrine complaint. A detailed summary of endocrine disorders and the syndromes in which these can be found is reported in Table 2.

Among endocrine abnormalities, we not only include specific conditions such as diabetes, hypogonadism or hypothyroidism, but also more general auxological issues, as short or tall stature or obesity. The pathogenesis of both the specific and the more general endocrine manifestations may differ among syndromes and is often not fully understood. The aim of this review is not to classify the endocrinological issues based on their pathogenesis, but rather to offer a practical schematic guide for the pediatrician. We therefore consider as endocrine manifestations both specific problems and more general clinical issues, these latter being the most common reasons for referral to the pediatric endocrinologist's outpatient clinic.

From syndromes to endocrine issues

Down syndrome (DS)

Thyroid

The incidence of congenital hypothyroidism in the newborn population is 0.7% (28 times more frequent than in the general population). In some patients, however, neonatal hypothyroidism is transient and follow-up is always recommended (Fort et al., 1984). In the light of the increased presence of beta-adrenergic receptors on circulating monocytes in the subset of DS patients with congenital hypothyroidism, one of the possible mechanisms could be associated to the increase in beta adrenergic receptors on thyrocytes, which may result in down regulation of the TSH receptor and therefore hypothyroidism (Zung et al., 2005).

The risk of acquired thyroid diseases is increased in patients with DS (prevalence 4-18%) (Bull, 2011). Due to the difficulty in establishing a clinical diagnosis as a result of overlapping symptoms, thyroid function should be evaluated at 6 months of age and then yearly (Bull, 2011). However, hypothyroidism in DS should neither be over-diagnosed nor over-treated, since isolated raised TSH has frequently a self-limiting natural history without any need for treatment (Gibson et al., 2005).

Thyroid autoantibodies are found in 13-34% of patients with DS (Karlsson et al., 1998). The natural history of autoimmune thyroiditis in DS is unusual, with no female predominance and infrequent goiter. The disease may pursue a fluctuating course between hypo- and hyperthyroidism (Popova et al., 2008).

Hyperthyroidism – mainly caused by Graves' disease – is 33 times more prevalent in DS patients than in the general population (0.66%), without gender preponderance. Antithyroid medications are often insufficient to attain remission and radioactive iodine is typically needed as a definitive treatment.

The predisposition to autoimmunity of DS individuals (autoimmune thyroid disease as well as type 1 diabetes) seems to be due to the decreased expression of the AIRE gene in the thymus, which results in the decrease in presentation of self-antigens in the thymic medulla, allowing persistence of T-cells directed against self-antigens (Giménez-Barcons et al., 2014).

Glucose metabolism

The prevalence of diabetes mellitus has been found to be increased in patients with DS in comparison with the general population (Bergholdt et al., 2006), with type 1 diabetes (T1D) being more frequent than type 2 (T2D) (Gillespie et al., 2006) .

The average age at the onset of T1D in DS individuals is also lower than in the background population (Bergholdt et al., 2006; Gillespie et al., 2006). As the symptoms of diabetes may be more difficult to detect and there is an increased risk of complications, polydipsia and polyuria always require special attention. Young DS patients with diabetes have better metabolic control, despite their intellectual impairment, probably as a result of a less complex lifestyle (Rohrer et al., 2010).

With regards to T2D, children with DS have reduced resting metabolic rates which contribute to obesity being more prevalent in these subjects than in other individuals (Hill et al., 2013). A lifelong regimen to monitor growth and prevent obesity should begin at 24 months of age and should include interventions on dietary behaviors and physical activity, since diabetes and

cardiovascular diseases are among the causes of premature mortality in DS (Day et al., 2005).

Stature

Short stature is a typical feature, and growth velocity is markedly reduced, mainly between the ages of 6 months and 3 years. Puberty tends to occur early, and the pubertal growth spurt is impaired. Final height is usually about 18 cm below the target height (Arnell et al., 1996). At present, treatment with recombinant human GH (rhGH) is not recommended in children with Down syndrome who have not been diagnosed with GH deficiency (Annerén et al., 2000).

Turner syndrome (TS)

Stature

Short stature affects 95–100% of individuals with TS, with average adult height 20 cm shorter than that of their peers. This is supposed to be caused by smaller (even though normal) size at birth, diminished growth rate starting at an early age, and a stunted growth spurt at puberty (Even et al., 2000). Most women with TS inherit just one copy of the *SHOX* gene. This state of haploinsufficiency seems to be substantially responsible for the height deficit in these patients (Guedes et al., 2008). Nevertheless, the haploinsufficiency of the *SHOX* gene does not explain all the anomalies in TS which are absent in isolated *SHOX* deficiency, suggesting that other genes take part in this process (Oliveira and Alves, 2011). Although GH production is essentially normal (a relative deficiency had been described in pubertal patients only) (Ross et al., 1985), treatment with rhGH has been approved in the USA and in Europe and is now

routinely used in several countries, with a gain in height of 8.5 cm above expected height (Soriano-Guillen et al., 2005). On the other hand, treatments with estrogen at low dosage during childhood (Ross et al., 2011) and oxandrolone (Sheanon and Backeljauw, 2015) are still debated.

Girls with otherwise unexplained short stature should have karyotype determined to rule out TS, since some girls with TS have short stature as the only recognizable feature.

Puberty and fertility

Clinical presentation of TS includes primary hypogonadism, whether occurring before or after puberty (gonadal dysgenesis). The degree of the dysfunction and the extension of gonadal defects are variable. When patients enter puberty spontaneously, progressive premature ovarian failure will follow in most cases (Mortensen et al., 2009). Nonetheless, nearly 20% of patients will present spontaneous menarche, with non-assisted pregnancy rate being 2% to 5% (Gravholt, 2005).

Karyotyping should thus be performed not only in the case of delayed puberty, but for primary amenorrhea and primary ovarian failure under the age of 30 as well.

Potential spontaneous puberty needs to be monitored by physical examination, while the assessment of FSH levels should begin at about age 10 (Bondy, 2009). Estrogen replacement therapy (ERT) is required for uterine development and bone mass acquisition in women with TS suffering from ovarian insufficiency (Nakamura et al., 2015).

Thyroid

Hypothyroidism develops in 10-30% of TS patients and is usually caused by autoimmune thyroiditis, with a prevalence that ranges from 13.3 to 55% (Medeiros et al., 2000). Variations

in TSH and/or thyroid hormones are often transient, recurrent and asymptomatic.

Glucose metabolism

T2D is 2–4 times more common in women with TS compared with the general population (Gravholt et al., 1998) and tends to develop at a younger age. An early metabolic defect in glucose uptake has been demonstrated, which results in reduced insulin sensitivity and hyperinsulinemia, and this may explain the high incidence of glucose intolerance in TS (Caprio et al., 1991). This is independent of body mass index, although obesity, a common problem in TS,(Elsheikh and Conway, 1998) will aggravate the insulin resistance. The cause of obesity in females with TS is unknown, but may be related, in part, to estrogen deficiency (Elsheikh et al., 2002). The increased risk (relative risk: 11.6) of T1D may be attributed to autoimmune predisposition (Elsheikh et al., 2002).

Klinefelter syndrome (KS)

Puberty and fertility

Micro-orchidism in KS syndrome is due to the degeneration of the seminiferous tubules. While germ cells are reduced in number, Leydig cell are preserved in their development. As a result, the onset of puberty is spontaneous in the majority of boys with KS, with a tendency for testosterone concentrations to decline at late adolescence/early adulthood (Wikström et al., 2006). The reduction in androgen production does not allow a complete development of secondary sexual characteristics, resulting in sparse facial, body and sexual hair and also in possible eunuchoidism and gynecomastia (Smyth and Bremner, 1998). While testosterone

treatment is rarely required to induce puberty, a supplementation may be needed in adulthood.

Although until recently KS patients were considered untreatably infertile, the introduction of testicular sperm extraction (TESE) combined with intracytoplasmic sperm injection (ICSI) has increased the chance of fathering a child (Aksglaede and Juul, 2013). The likelihood of finding motile sperm in the ejaculate may be higher in semen samples from early pubertal KS individuals (Aksglaede and Juul, 2013). Few cases of paternity without assisted medical technology have been reported, usually with a mosaic karyotype.

Stature

Tall stature in KS is linked to an overexpression of SHOX gene, since height increases with the number of extra X or Y chromosomes (Ottesen et al., 2010), although stature in males with 49,XXXXY syndrome is usually below average (Tartaglia et al., 2011). The increment in stature is most pronounced between ages 5 and 8, with the development of long arms and legs and short torso, reaching an average adult height of 179.2 ±6.2 cm (Schibler et al., 1974).

Glucose metabolism

Hypogonadism in KS may cause unfavorable changes in body composition, primarily through increased truncal fat and decreased muscle mass. The prevalence of metabolic syndrome is increased in KS, while insulin sensitivity is decreased. Testosterone treatment prevents this condition by inducing reduction of insulin levels in parallel with a decrease of fat tissue mass (Bojesen et al., 2006).

Thyroid

Some studies have suggested that thyroid abnormalities (hypothyroidism, thyroiditis) may be common, but this has not been fully verified (Bjørn et al., 2009).

Prader-Willi syndrome (PWS)

Stature

The prevalence of GH deficiency in PWS ranges from 40-100% depending on the test and the cut-off level (Burman et al., 2001; Diene et al., 2010). In addition to short stature despite obesity, low IGF-1 and decreased GH secretion on stimulation tests, also abnormal body composition is coherent with GH insufficiency (Deal et al., 2013).

Therapy with rhGH in PWS children was approved in the USA in 2000 and in Europe in 2006, and is now used for other benefits besides increased stature, including increased muscle mass and decreased body fat, better lipid profile, improved strength, agility and motor development; these changes appear to be greatest within the first year of therapy (Festen et al., 2008). Some trials have reported an additional positive effect on cognitive development (Siemensma et al., 2012).

No consensus has been reached on the optimal age for starting treatment. However, usually rhGH therapy is started before the onset of obesity, which often occurs by age 2; some experts recommend starting as early as 3 months of age (Deal et al., 2013).

Concerns have been raised with respect to the relationship of rhGH with extremely high IGF-1 levels, glucose intolerance, scoliosis, sleep-disordered breathing and sudden death.

An increase in risk of sudden death has been reported in children with PWS, independent of GH therapy and probably related to the increased risk of central adrenal insufficiency (in

particular during acute respiratory illness) (Tauber et al., 2008). No differences were found in mortality rates between children receiving treatment and those who did not.

Current recommendations are to have polysomnography and an otorhinolaryngologic examination, or tonsillectomy in the case of enlarged tonsils, before starting rhGH treatment; to monitor IGF-1 levels every 6-12 months; and to aggressively treat upper airway infections (Angulo et al., 2015; Whitman and Myers, 2013).

Adrenal response to stress

Isolated ACTH insufficiency is rare, but it may be a component of multiple hormone deficiencies. As a result of generalized hypothalamic dysfunction, children and adults with PWS are at risk for central adrenal insufficiency (CAI). While one cross-sectional analysis reported CAI in 60% of cases after administration of an overnight single-dose of metyrapone, five subsequent studies using different methodologies did not confirm this frequency (Angulo et al., 2015). The true prevalence of CAI in PWS remains therefore unclear and there is still no consensus on the proper evaluation of CAI and/or preoperative treatment or during significant stress.

Puberty and fertility

Hypogonadism represents a common clinical feature in PWS. Both males and females with PWS are affected by hypogonadism. Males usually have undescended testes (80-90%), with hypopigmented, hypoplastic scrotum, and may have micropenis (Cassidy et al., 2012); female hypoplasia of clitoris and labia minora may be unnoticed on physical examination. Similar to many other manifestations of PWS, hypogonadism has been classically thought to be of hypothalamic etiology. However, recent evidence has emerged supporting primary gonadal

failure as a significant contributor to male hypogonadism. Other studies have also shown a combined picture of hypogonadotropic hypogonadism with relatively low LH levels, and primary hypogonadism with low inhibin B and relatively high FSH levels (Radicioni et al., 2012).

Since delayed and/or incomplete puberty is a common characteristic, many patients require treatment to induce or maintain puberty (Goldstone et al., 2008). However, precocious adrenarche (15-30%) and precocious puberty (4%) have also been reported in PWS patients (Crinò et al., 2003).

No consensus statement exists on the most appropriate regimen of hypogonadism treatment in PWS. The choice of a particular hormone replacement therapy protocol will depend on the age at diagnosis and local practices. However, orchidopexy is often required to ensure a stable position in the scrotum in males (Angulo et al., 2015).

Induction of menses have been reported with the use of selective serotonin reuptake inhibitor (SSRI) which appears to modulate pulsatile hypothalamic GnRH secretion, providing arguments against an intrinsic complete GnRH deficiency in PWS (Åkefeldt et al., 2007).

While there have been no reports of paternity so far, 4 pregnancies have been documented in females with PWS (2 of the children presented Angelman syndrome).

Thyroid

The prevalence of hypothyroidism is variable (from 2 to 70%) and cannot be clearly established. Low levels of fT4 in the presence of normal TSH suggest a central origin. During rhGH therapy fT4 levels drop considerably, due to increased peripheral conversion of fT4 to fT3 promoted by rhGH, while fT3 levels do not vary (Festen et al., 2007).

Screening with fT4 and TSH should be performed in the first three months of life and then

once-yearly, particularly if the patient is receiving rhGH (Angulo et al., 2015).

Glucose metabolism

T2D has been reported in one out of four adults with PWS (mean age at onset: 20 years) (Butler et al., 2002), but is much less frequent in children. Screening for diabetes and metabolic syndrome should be performed in obese patients (as in all obese individuals). An evaluation of diabetes risk should be performed before starting rhGH and during treatment in obese patients over 12 years of age (Deal et al., 2013). However, pediatric studies have not shown significant alterations in glucose homeostasis after up to four years of rhGH treatment (de Lind van Wijngaarden et al., 2009).

Noonan syndrome (NS)

Stature

Together with heart defects, short stature is one of the major criteria to diagnose NS (van der Burgt, 2007). While birth length is generally normal, failure to thrive is often evident from the first year of life, usually following the 3rd centile thereafter (Otten and Noordam, 2009). At puberty, growth velocity is below the mean and the growth spurt is attenuated. Since bone maturity is usually delayed, growth is likely to extend into the twenties. Final adult height is within the normal adult range in 30% of NS individuals, while more than 50% of females and nearly 40% of males have a short final stature (Noonan et al., 2003). Decreased IGF-1 and IGF-BP3 and low peaks in provocation tests, suggest impaired GH release or alteration of the GH/IGF-1 axis. In some patients, a mild GH resistance related to a post-receptor signaling defect has been reported (Binder et al., 2005).

Treatment with rhGH (in pharmacological doses) has been approved in the USA since 2007, while no indications are available yet for Europe. Reports on long-term effects support the hypothesis of a benefit of rhGH therapy (Osio et al., 2005), but high-quality controlled trials on the impact on adult height are lacking (Giacomozzi et al., 2015).

Puberty and fertility

In male patients, cryptorchidism is common (77%) at birth, LH and FSH are increased in prepubertal period, and high FSH and poor quality semen have been found in adults, suggestive of failure of spermatogenesis after testicular maldescent (Elsawi et al., 1994). In both males and females, puberty is delayed by nearly 2 years and the growth spurt is frequently reduced or missing. In female patients, mean age at menarche is 14.6 years, but fertility is not impaired (Sharland et al., 1992). On the contrary, in male patients, subfertility has been suggested to be connected not only to cryptorchidism to Sertoli cells dysfunction as a result of the genetic defects itself. A recent retrospective study (Moniez S et al., 2018) reported significant lower levels of AMH and inhibin B in NS compared to the general population, without difference between cryptorchid and non-cryptorchid patients. Lower AMH and inhibin B levels were found in NS-PTPN11 patients, whereas in SOS1 patients these markers did not differ from healthy children.

Thyroid

Thyroid antibodies are common, but hypothyroidism is as frequent as in the general population (Vesterhus and Aarskog, 1973). Follow-up to evaluate thyroid function and autoimmune status should be performed every 3 to 5 years.

From endocrine issues to syndromes

Adrenal insufficiency

Adrenal insufficiency is fairly rare in children and adolescents. Since signs and symptoms may be unspecific, early diagnosis of the condition may be difficult. Patients with chronic adrenal insufficiency usually complain of, among other symptoms, chronic fatigue, which may mimic other illness, including endocrine disorders. However, if unrecognized, they may present life-threatening cardiovascular collapse (Shulman et al., 2007).

The rate of adrenal insufficiency caused by genetic syndromes (i.e. Triple A, IMAGE, Wolman, Zellweger) varies from 4 to 15% (Perry et al., 2005; Simm et al., 2004). In the case of autoimmune adrenalitis, it is part of an autoimmune polyendocrine syndrome (APS), in 60% of patients (Betterle, 2002).

Pseudo-precocious puberty

In girls, autonomous functional ovarian follicular cysts are the most frequent reason of pseudo-precocious puberty, mostly self-limiting and not requiring treatment. However, when cysts are recurrent, the prolonged or repeated exposure to estrogens can trigger early maturation of the hypothalamic-pituitary-gonadal axis, resulting in gonadotropin-dependent precocious puberty (de Sousa et al., n.d.).

Autonomous ovarian cysts might also be an early manifestation of the McCune-Albright syndrome (MAS) (30%). This syndrome – with an estimated prevalence between 1/100,000

and 1/1,000,000 – is classically identified by the clinical triad of polyostotic fibrous dysplasia, *café-au-lait* skin pigmentation (with jagged "coast of Maine" borders), and pseudo-precocious puberty. *Café-au-lait* spots are the most common "presenting" sign, often unnoticed, even though usually present at birth or shortly thereafter (Dumitrescu and Collins, 2008). Moreover, pseudo-precocious puberty may arise before the emergence of spots or bone lesions which can increase over time and may be absent at the initial presentation (Fritz and Speroff, 2011). Therefore a diagnosis of MAS should be suspected in girls presenting with recurrent functional ovarian follicular cysts and episodic menses (Frisch et al., 1992), considering that partial forms of the syndrome also have been described (Lumbroso et al., 2004). The average age of the pubertal onset in MAS is three years; however, vaginal bleeding has been reported in females as young as four months. As in other forms of pseudo-precocious puberty, the sequence of pubertal development may be abnormal (i.e. vaginal bleeding frequently precedes breast development). Pseudo-precocious puberty could also be present in boys (although less frequent and later) as bilateral or even monolateral testicular enlargement. MAS is also associated with a number of hyperfunctioning endocrinopathies (see Table 1) (Dumitrescu and Collins, 2008).

Hypoparathyroidism

Hypoparathyroidism in infancy is usually transient and linked to delayed maturation of the parathyroid gland. When prolonged, it is often due to an error in the embryogenesis of the parathyroid glands. In approximately 70% of children with isolated hypoparathyroidism the cause is the 22q11.2 deletion syndrome (22q11DS) (also known as Di-George or velo-cardio-facial syndrome) (McDonald-McGinn and Sullivan, 2011).

Because of the significant variability of expression, especially in the absence of classic findings, the diagnosis may be missed (Bassett et al., 2005). Neonates with severe hypocalcemia and apparent hypoparathyroidism should be further evaluated for adequacy of parathyroid secretion, and should undergo examination for specific 22q11DS features (such as heart defect, palatal abnormalities, characteristic facial features, immune deficiency) which may not be readily apparent (Greig et al., 1996). Even if it is a rare initial isolated clinical manifestation (2.5%), neonatal hypocalcemia caused by hypoparathyroidism is one of the cardinal symptoms of 22q11DS (43%, but likely underestimated because blood calcium levels are usually tested only in symptomatic patients), mostly when only minor cardiac anomalies are present.

When diagnosis is made before 2 years of age, cardiac defects may still not be the signs leading to the final diagnosis (44%) (Cancrini et al., 2014). Cases of 22q11DS with resolution of hypoparathyroidism in infancy and recurrence of hypocalcemia with permanent hypoparathyroidism in later childhood have also been described (Greig et al., 1996).

Hyperinsulinism

Persistent hyperinsulinism in infancy may be caused by several molecular alterations (such as defects of K-ATP channel, increased activity of beta-cell glucokinase or glutamate dehydrogenase) (Meissner et al., 1999), but is often unrelated to well-defined genetic defects. Furthermore, nearly 10% of patients with neonatal persistent hyperinsulinism have other significant clinical symptoms, suggesting an underlying syndrome, including congenital disorders of glycosylation, Usher 1C syndrome or Beckwith-Wiedemann syndrome (BWS), Turner syndrome and Sotos syndrome (Meissner et al., 2001).

BWS is a congenital overgrowth syndrome caused by dysregulation of imprinted growth regulatory genes within the chromosomal 11p15 region. The phenotype is characterized by prenatal and/or postnatal overgrowth, macroglossia, anterior abdominal wall defects, organomegaly, hemihypertrophy, ear lobe creases and helical pits, and renal tract abnormalities.

Although BWS is a relatively uncommon cause of neonatal hyperinsulinemic hypoglycemia, its incidence in children with BWS is about 50% (Elliott et al., 1994). In the majority of infants, hypoglycemia is transient, mild and asymptomatic; however, in about 5% of children, it may persist after the neonatal period, requiring medical therapy. Newborn with BWS can develop persistent hyperinsulinemic hypoglycemia within 24 hours after birth when obvious clinical features of syndrome may still not be present (Hussain et al., 2005). Persistent hyperinsulinism in syndromic children is well responsive to diazoxide therapy.

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Figure 1. Syndromes with prevalence higher than 1:10000 and commonly associated with endocrine manifestations, placed according to frequency of presentation type (whether with endocrinological or dysmorphic signs).

Table 1. Syndromes associated with endocrinopathies (from syndromes to endocrine issues)

22q11.2 deletion syndrome	Hyperthyroidism Hypoparathyroidism Hypothyroidism Obesity Short stature
3M syndrome	Hypergonadotropic hypogonadism (male) Short stature
Aarskog syndrome	Short stature
Alström syndrome	Obesity Diabetes mellitus (insulin resistance/deficiency)
APS 1 (or APECED or Whitaker syndrome)	Adrenal insufficiency Hypoparathyroidism
APS 2 (or Schmidt syndrome)	Adrenal insufficiency Autoimmune thyroiditis Diabetes mellitus (type 1) Hypergonadotropic hypogonadism
Bardet-Biedl syndrome	Diabetes insipidus (nephrogenic) Diabetes mellitus (insulin resistance/deficiency) Hypogonadotropic hypogonadism Obesity
Beckwith-Wiedemann syndrome	Hyperinsulinism Tall stature
CHARGE syndrome	Hypogonadotropic hypogonadism Short stature
Cohen syndrome	Obesity
Cornelia de Lange syndrome	Short stature
Down syndrome	Autoimmune thyroiditis Diabetes mellitus (Type 1) Hypothyroidism Short stature
Fragile X syndrome	Tall stature
IMAGE syndrome	Adrenal Insufficiency Hypogonadotropic hypogonadism
Kabuki syndrome	Diabetes insipidus (central) Short stature
Kallmann syndrome	Hypogonadotropic hypogonadism Hypothyroidism
Klinefelter syndrome	Diabetes mellitus (Type 1 and insulin resistance/deficiency) Hypergonadotropic hypogonadism Hypothyroidism Tall stature
Laurence-Moon syndrome	Hypogonadotropic hypogonadism
Marfan syndrome	Tall stature
McCune-Albright syndrome	Hypercortisolism (ACTH independent)

	Hyperthyroidism Pseudo-precocious puberty Tall stature
Noonan syndrome	Hypergonadotropic hypogonadism Short stature
Pallister-Hall syndrome	Hypothyroidism
Patau-Edwards syndrome	Short stature
Pendred syndrome	Hypothyroidism
Prader-Willi syndrome	Adrenal Insufficiency Diabetes mellitus (insulin resistance/deficiency) Hypogonadotropic hypogonadism Hypothyroidism Precocious puberty Obesity
Robinow syndrome	Hypergonadotropic hypogonadism
Russell-Silver syndrome	Precocious puberty Short stature
Seckel syndrome	Short stature
Smith-Lemli-Opitz syndrome	Adrenal Insufficiency Hypergonadotropic hypogonadism Short stature
Sotos syndrome	Tall stature
Triple A (or Allgrove) syndrome	Adrenal Insufficiency
Turner syndrome	Diabetes mellitus (Type 1 and insulin resistance/deficiency) Autoimmune thyroiditis Hypergonadotropic hypogonadism Hypothyroidism Short stature
Van Wyk-Grumbach syndrome	Hypothyroidism Pseudo-precocious puberty
Williams-Beuren syndrome	Diabetes mellitus (Type 2 and insulin resistance/deficiency) Hypercalcemia (Hypervitaminosis-D) Hypothyroidism Precocious puberty Short stature
Wolfram syndrome (DIDMOAD)	Diabetes insipidus (central) Diabetes mellitus (defects of beta cell function)
Wolman syndrome	Adrenal Insufficiency
X-Linked Adrenal Hypoplasia Congenita	Adrenal Insufficiency Hypogonadotropic hypogonadism
Zellweger syndrome	Adrenal Insufficiency

Table 2. Endocrinopathies that can expose a syndrome (from endocrine issues to syndromes)

Adrenal insufficiency	APS 1 APS 2 IMAGE syndrome Prader-Willi syndrome Smith-Lemli-Opitz syndrome Triple A (or Allgrove) syndrome Wolman syndrome X-Linked Adrenal Hypoplasia Congenita Zellweger syndrome
Diabetes insipidus (central)	Kabuki syndrome Wolfram syndrome (DIDMOAD)
Diabetes insipidus (nephrogenic)	Bardet-Biedl syndrome
Diabetes mellitus	Alström syndrome (insulin resistance/deficiency) APS 2 Bardet-Biedl syndrome (insulin resistance/deficiency) Down syndrome (Type 1) Klinefelter syndrome (Type 1 and insulin resistance/deficiency) Prader-Willi syndrome (insulin resistance/deficiency) Turner syndrome (Type 1 and insulin resistance/deficiency) Williams-Beuren syndrome (insulin resistance/deficiency) Wolfram syndrome (DIDMOAD) (defects of beta cell function)
Autoimmune thyroiditis	APS 2 Down syndrome Turner syndrome
Hypercortisolism (ACTH independent)	McCune-Albright syndrome
Hypergonadotropic hypogonadism	3M syndrome (male) APS 2 Klinefelter syndrome Noonan syndrome Robinow syndrome Smith-Lemli-Opitz syndrome Turner syndrome
Hyperinsulinism	Beckwith-Wiedemann syndrome
Hyperparathyroidism/ Hypercalcemia	McCune-Albright syndrome Williams-Beuren syndrome
Hyperthyroidism	22q11.2 deletion syndrome

	Down syndrome McCune-Albright syndrome
Hypogonadotropic hypogonadism	Bardet-Biedl syndrome CHARGE syndrome IMAGE syndrome Kallmann syndrome Laurence-Moon syndrome Prader-Willi syndrome X-Linked Adrenal Hypoplasia Congenita
Hypoparathyroidism	APS 1 22q11.2 deletion syndrome
Hypothyroidism	22q11.2 deletion syndrome Down syndrome Klinefelter syndrome Pallister-Hall syndrome Pendred syndrome Prader-Willi syndrome Turner syndrome Van Wyk-Grumbach syndrome Williams-Beuren syndrome
Obesity	22q11.2 deletion syndrome Alström syndrome Cohen syndrome Bardet-Biedl syndrome Prader-Willi syndrome
Precocious puberty	Prader-Willi syndrome Russell-Silver syndrome Williams-Beuren syndrome
Pseudo-precocious puberty	McCune-Albright syndrome Van Wyk-Grumbach syndrome
Short stature	22q11.2 deletion syndrome 3M syndrome 18q deletions Aarskog syndrome CHARGE syndrome Cornelia de Lange syndrome Down syndrome Kabuki syndrome Noonan syndrome Patau-Edwards syndrome Russell-Silver syndrome Seckel syndrome Smith-Lemli-Opitz syndrome Turner syndrome Williams-Beuren syndrome
Tall stature	Beckwith-Wiedemann syndrome Fragile X syndrome

	Klinefelter syndrome Marfan syndrome McCune-Albright syndrome Sotos syndrome

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