Hypoparathyroidism in Children

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Abstract

This chapter focuses on the rare disorder of hypoparathyroidism in children. It details the clinical features, pathophysiology, and biochemical abnormalities of the many forms seen clinically. Up-to-date information about the genetics of these disorders is provided along with the abnormalities in gene function. The chapter concludes with a summary of current treatment options for children with these disorders.

Keywords

Hypoparathyroidism • Ionized calcium • Hypocalcemia • Parathyroid hormone • Distal renal tubular reabsorption • Urinary calcium • Renal 1 alpha hydroxylase • 1,25 Dihydroxy vitamin D • Seizures • Laryngospasm • Cardioversion disturbances • Neuromuscular irritability • Currently • Paresthesias • Chvostek sign • Trousseau sign • Mental retardation • Dental hypoplasia • Psychological manifestations • Radiological signs • Metaphysis • Basal ganglia • Calcifications of basal ganglia • FARR syndrome • Phosphatemia • Hypomagnesemia • Embryological development • Transcription factors • Calcium sensing receptors • DiGeorge syndrome • Fluorescent in situ hybridization • TBX.1 gene • Microcephaly • Hypertelorism • Cleft palate • Micrognathia • Philtrum • Thymic aplasia • Immunological disorders • Urogenital, skeletal, ocular malformations • Behavioral problems • Glial cell missing B transcription factor • Hypoparathyroidism • Deafness • Renal dysplasia syndrome • Hypoparathyroidism • Retardation • Dysmorphism • Kenny-Caffey syndrome

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• Sanjad–Sakati syndrome • Familial hypoparathyroidism X linked length recessive transmission • SOX3 • Deficiency of PTH production • Heart is normal dominant hypocalcemia • G protein coupled receptors • Activating and inhibiting mutations • Pseudo-Bartter syndrome • Mutation in PTH gene • Mitochondrial disease • Kearns–Sayre syndrome • Acquired hypoparathyroidism • Calcium receptor antibodies • APECED syndrome • NA LP 5 protein • Surgery • Maternal hyperparathyroidism and neonatal hypoparathyroidism • Iatrogenic causes of hypocalcemia • Antiepileptic drugs • Ketoconazole • Aluminum hydroxide • Laxatives • Acute pancreatitis • Rhabdomyolysis • Treatment • Increased urinary calcium excretion • Nephrocalcinosis • Calcium chelators • Septic shock • Infectious syndromes • Chemotherapy • Invasive tumors • Alfacalcidol • Lithiasis • Exogenous PTH • Teriparatide • Osteosarcoma • Autosomal dominant hypoparathyroidism • Cytochrome P450

Introduction

Hypoparathyroidism is a rare disorder due to a deficient secretion of parathyroid hormone (PTH) by the parathyroid glands, and hence the incapacity to maintain normal extracellular ionized calcium levels. It may cause clinical symptoms which upon further investigation will show hypocalcemia, hyperphosphatemia, and an inappropriately low PTH level. In contrast to hypoparathyroidism in adulthood, usually secondary to thyroid surgery, hypoparathyroidism in childhood is mostly due to a congenital disorder, even if symptoms are not present during the neonatal period. In most cases, the diagnosis is made or suspected during infancy or puberty. Those periods are marked by an increase in growth velocity and therefore an increase in calcium requirements. As a consequence, mild or persistent hypocalcemia may become symptomatic.

Clinical Features

Symptoms

Whatever the cause, the symptoms of hypoparathyroidism are due to hypocalcemia. Deficient PTH secretion prevents resorption of calcium from the skeleton and diminished absorption of intestinal calcium due to decreased production of 1,25 dihydroxyvitamin D (from lower activity of renal 1α-hydroxylase), and decreased renal tubular reabsorption.

Symptoms of hypocalcemia vary with age and acuteness of the disease. Hypocalcemia can manifest acutely through generalized seizures, laryngospasm, and cardiac rhythm disturbances. However, symptoms may be milder and nonspecific: neuromuscular irritability (tetany, muscles cramps, paresthesia, increased muscular contractility assessed by Chvostek's sign and Trousseau's maneuver), cardiac rhythm disturbances, attention deficit disorders, poor academic performance, mental retardation, poor dental condition such as enamel hypoplasia. In rare cases, hypocalcemia may be found on routine blood screening for unrelated issues. In older children, hypocalcemia may present as psychological manifestations (depression and sleeping disturbances).

Biochemistry

In patients affected with hypoparathyroidism, serum calcium is low (<2.2 mM), by definition less than the lower limit of the reference laboratory being used. Whatever the age, ionized calcium is also reduced to less than 1 mM. PTH levels are low, often undetectable, or inappropriately normal in presence of hypocalcemia (the absence of PTH rise in response to hypocalcemia asserts the hypoparathyroidism). Because calcium

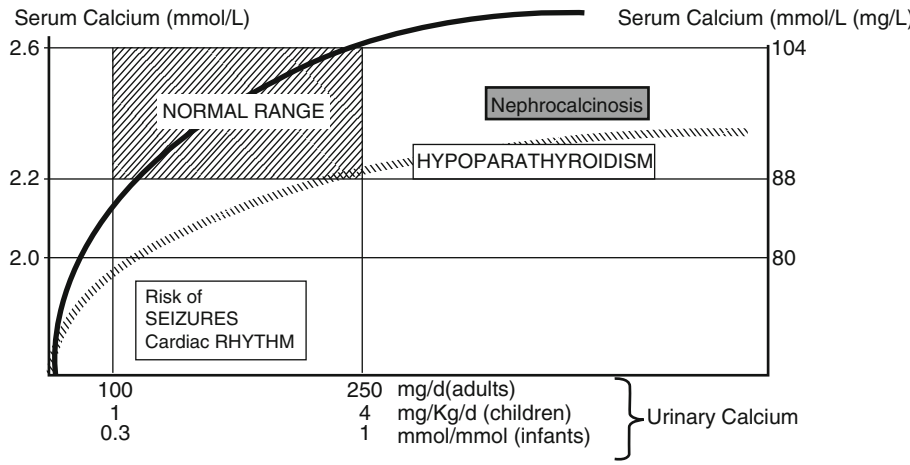

Fig. 16.1 Clinical consequences of hypocalcemia in presence of hypoparathyroidism. Because of PTH lack, relationship between serum and urinary calcium is lowered and shifted toward the right (normal condition: *black line*; hypoparathyroidism: *dotted line*). Therefore, nephrocalcinosis would rapidly appear for lower serum calcium values than in healthy patient

levels are low, the urinary calcium excretion is usually low or undetectable at the time of diagnosis. However, elevated urinary calcium excretion can be found in some rare cases of hypoparathyroidism due to an activation of the calcium sensing receptor (CaSR) or in patients with low–normal calcium levels (Fig. 16.1).

Serum phosphorus is elevated due to the deficient excretion of phosphates in absence of PTH. This observation is often confounded by the natural occurrence of higher levels of phosphorus in infants and young children, but attention to the ambient calcium helps determine the significance. Magnesium levels are normal or low–normal in patients with hypoparathyroidism. However, severe hypomagnesemia, found in patients affected with a genetic defect in magnesium transport, impairs the PTH secretion and mimics the genetic causes of hypoparathyroidism. Although vitamin D levels (25-OH vitamin D) are often low at the time of diagnosis, this alone is not sufficient to cause the symptoms since the normal physiological response to vitamin D deficiency is an increased secretion of PTH and production of hydroxylated vitamin D. Obviously, this counterresponse to low vitamin D and serum calcium is impaired in patients with hypoparathyroidism leading to hypocalcemia.

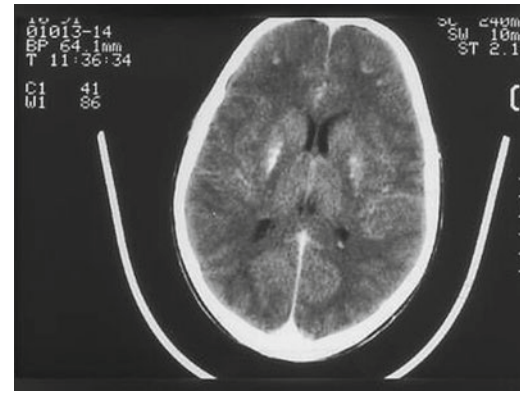

Fig. 16.2 Farr syndrome

Radiological Findings

Because PTH is involved in bone turnover, PTH deficiency, as seen in hypoparathyroidism, is associated with an increase in bone density, dense metaphyseal striae, and cortical thickening [1] (Fig. 16.2). Calcifications of the basal ganglia or widespread calcifications in other intracranial structures assessed through computed tomography imaging of the head may be associated with chronic hypocalcemia (Fahr syndrome) [2].

Causes of Hypoparathyroidism

The mechanisms leading to hypoparathyroidism are numerous: impairment of the embryonic development of the parathyroid glands, abnormal regulation of the PTH synthesis and/or secretion, or acquired injury of the parathyroid glands. Some of the genetic determinants of parathyroid glands embryogenesis, PTH synthesis and secretion, or autoimmunity are now known (Table 16.1).

Impaired Embryonic Development of the Parathyroid Glands

Animal studies have shown that embryogenesis of the parathyroid glands is controlled through a genetic cascade comprising different transcription factors (Hoxa3-Pax1/9-Eya1-Six1/4-Shh-Tbx1-Gcmb2-CCL21), the CaSR, and the PTH [3]. Mutations in those genes cause hypoparathyroidism during infancy or early in childhood.

DiGeorge Syndrome

To date, the DiGeorge syndrome is the most frequent cause of hypoparathyroidism among the embryologic anomalies of the parathyroid glands (around 1/4,000 living births). It is responsible for congenital hypoplasia, or agenesis of the parathyroid glands and thymus. A recurrent large hemizygotic deletion of the 22q11.21-q11.23 region, removing about forty genes, is identified by fluorescent in situ hybridization (FISH) in more than 95% of the patients affected with DiGeorge syndrome. In addition to this autosomal dominant transmission, the deletion may occur de novo [4].Patients affected with the DiGeorge syndrome without the 22q11.21-q11.23 deletion

Table 16.1 Etiologies of hypoparathyroidism

Syndrome	Transmission	Gene(s); chromosome	Alteration	Clinical symptoms
APECED	RA	AIRE; 21q22.3	Immunologic tolerance	Neonatal candidosis, hypoparathyroidism (6–7 years), Addison disease (12–15 years)
DiGeorge (CATCH-22)	Sporadic/DA	rnex40/nex2,2, TBX1 UDFL1; 22q11	Branchial pouches	Dysmorphy, thymus agenesis, heart malformations, immunological abnormalities, mental retardation
Kearns–Sayre	Maternal/ sporadic	Mitochondrial DNA	Energy production	Isolated hypoparathyroidism, mitochondrial disease
Kenny-Caffey	RA	TBCE; 1q42-q43	Tubulin chaperone	Osteosclerosis, short stature, eyes abnormalities
Sanjad–Sakati	RA	TBCE; 1q42-q43	Tubulin chaperone	Short stature, mental retardation
Hypoparathyroidism deafness, renal defect (HDR)	DA	GATA3; 10p14-10p15.1	TF embryologic development	PT agenesis or hypoplasia, neurosensorial deafness, renal dysplasia
Hypoparathyroidism, retardation, dysmorphia (HRD)	RA	TBCE; 1q42-q43	Tubulin chaperone	Mental retardation, microcephaly, IUGR, micropenis, dysmorphy
Autosomal dominant hypocalcemia	DA	CaSR; 3q13.3-q21	PTH synthesis	Unadapted urinary calcium excretion
Isolated hypoparathyroidism	DA/RA	PTH; 11q15.3-p15.1	PTH synthesis	
Isolated hypoparathyroidism	RA/DA	GCMB; 6p24.2	TF PT embryology	PT agenesis

APECED autoimmune endocrinopathy–candidiasis–ectodermal dystrophy, *CaSR* calcium-sensing receptor, *DA* dominant autosomal, *IUGR* intrauterine growth restriction, *RA* recessive autosomal, *TF* transmission factor, *TBCE* tubulin cofactor E, *PT* parathyroid gland

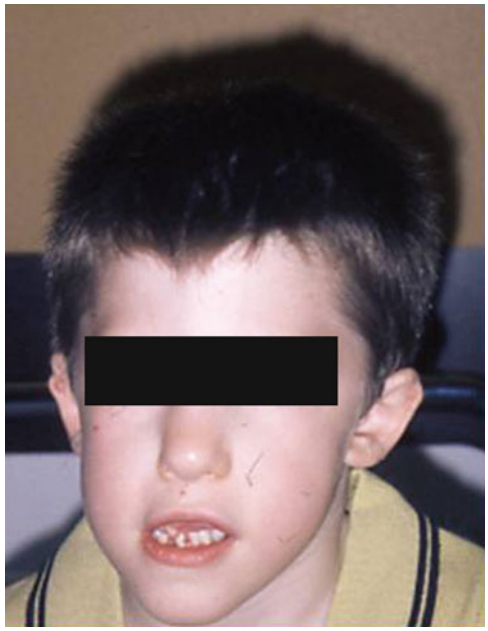

Fig. 16.3 Facial dysmorphia in DiGeorge syndrome

have been described. These patients carry mutations in the *TBX1* gene, located within the 22q11 region, suggesting that *TBX1* is responsible for the main features of the syndrome [5, 6]. Furthermore, a deletion in the 10p13-p14 region, close to the HDR (hypoparathyroidism, deafness, and renal dysplasia) syndrome locus, has been described in patients with a DiGeorge-like phenotype [7].

The phenotypical spectrum of the DiGeorge syndrome is wide and results from a developmental defect of the third and fourth pharyngeal pouches and the facial neural crest. According to the age at diagnosis, symptoms will be more or less prominent [8, 9].

- *Facial dysmorphia* includes microcephaly, narrow palpebral fissures, hypertelorism, small mouth, cleft palate, micrognathia, and smooth philtrum (Fig. 16.3).
- *Various congenital cardiac malformations* are frequent (80–85%). They are most often diagnosed during the fetal or neonatal period: aortic arch anomalies, tetralogy of Fallot, conotruncal anomalies such as truncus arteriosus, interrupted aorta, hypoplasia of the pulmonary artery. In both animal and humans, these defects are attributed to a deficiency inTBX1 [6, 10].
- *Hypoparathyroidism* due to the hypo- or aplasia of the parathyroid glands may be the sole clinical feature.
- *Infectious diseases* during early childhood are frequent because of thymic hypo- or aplasia.
- *Dysimmunity* (celiac disease, Graves' disease, and arthritis) may appear later in adulthood.
- *Malformations* can be present: urogenital (agenesis or renal dysplasia, multicystic kidney, obstructive uropathy, and cryptorchidism), skeletal (scoliosis), and ocular anomalies (coloboma, cataract, and microphthalmia).
- *Behavioral problems* (personality disturbances) have been attributed to the haploinsufficiency of the catechol-*O*-methyl transferase gene [11].

Follow-up of patients affected with the DiGeorge syndrome has to be adjusted to the patient's age: neonatal period—hypocalcemia, heart disease, eating problems; early childhood—hypocalcemia, heart disease, psychomotor retardation, infection; school age—infection, psychomotor retardation, personality disturbances; adult age—autoimmune diseases.

Hypoparathyroidism Associated with a Defect in the Glial Cell Missing B Gene

Glial cell missing B (GCMB) is a transcription factor initially identified in the Drosophila where it is necessary to glial cell differentiation. In mice, *Gcm1* is expressed in the placenta and *Gcm2* in the parathyroid glands and ovaries [3]. The identification of biallelic mutations or monoallelic dominant negative mutations in the *GCMB* gene in families with autosomal recessive and autosomal dominant neonatal hypoparathyroidism, respectively, has demonstrated the importance of GCMB for the embryogenesis and maintenance of parathyroid cells in humans [12–14]. *Gcm* probably contributes to the PTH synthesis by controlling the expression of the calcium sensing receptor [15, 16]

To summarize, mutations in the *GCMB* gene are found in patients affected with isolated hypoparathyroidism, especially when the disease is hereditary.

HDR Syndrome

HDR syndrome, also known as Barakat syndrome, is inherited as an autosomal dominant trait. Haploinsufficiency of GATA3, a member of the GATA family of transcription factors, either through a large deletion in the 10p14-10p15 region or through point mutations of the *GATA3* gene, is responsible for the disease [17–19]. Noteworthy, gene duplications have been also described [20]. GATA3 is a transcription factor belonging to the large GATA family. It is involved in the embryogenesis of the parathyroid glands, kidney, and internal ear, as well as in the differentiation of lymphocytes T_H1 and T_H2 [17].

Hypoparathyroidism secondary to a GATA3 mutation is often severe. Associated features allow the diagnosis of the syndrome [20] sometimes described as a pseudo DiGeorge syndrome: slanted palpebral fissures, hypertelorism, blepharophimosis, narrow nose root, anteverted nostrils, micrognathia, and arched palate. Other cardinal signs are required for the diagnosis: enlargement of the nipple distance, clinodactyly, syndactyly, hypotony, bilateral neurosensitive deafness and renal malformations: multicystic kidneys, nephrotic syndrome, renal dysplasia (hypoplasia), vesicoureteral reflux, chronic renal insufficiency, hematuria, proteinuria, and characteristic bone impairment.

Hypoparathyroidism Retardation Dysmorphism Syndrome

HRD syndrome (hypoparathyroidism retardation dysmorphism) unifies two previously described syndromes: the Kenny-Caffey syndrome, in its autosomal recessive form, and the Sanjad–Sakati syndrome, both due to a defect in the *TBCE* (Tubulin specific Chaperone E) gene, localized in 1q42-q43, and coding for a protein involved in the polymerization of the α and β tubulin subunits. This protein is allows the formation of intracellular microtubules; as a result of genetic abnormalities in the gene coding TBCE, a large amount of intracellular functions are impaired in affected patients [21]. In 4q35, a different gene is likely involved in a phenocopy of the HRD syndrome [22].This syndrome of autosomal recessive inheritance was initially described in the Bedouin families originating from Saudi Arabia affected with hypoparathyroidism and associated symptoms such as intrauterine growth restriction (80% of the cases), extreme growth retardation, mental retardation, microcephaly, facial dysmorphy including hollow eyes, pronounced nasal bridge, small turned-up nose, thin upper lip and micrognathy, short feet and hands, hypogonadism, susceptibility to infections, and dysimmunity [21, 23].

Familial Hypoparathyroidism of X-linked Recessive Transmission

Three American families have been reported as presenting a possible X-linked recessive transmission form of isolated hypoparathyroidism due to agenesis of the parathyroid glands. The patients presented with an X chromosome rearrangement involving the *SOX3* locus. Animal models have demonstrated the role of *SOX3* in the embryogenesis of parathyroid glands [24].

Deficiency in PTH Production and Secretion

Autosomal Dominant Hypocalcemia

Autosomal dominant hypocalcemia (ADH) was described in the 1990s following the cloning of the CaSR. CaSR is a transmembrane receptor belonging to the super family of G-protein coupled receptors (GPCR). The CaSR is expressed, among other tissues, on the cell surface membrane of the parathyroid cells and the renal tubular cells. Extracellular calcium ions are the main ligands of the CaSR. The CaSR controls the PTH synthesis as well as renal tubular calcium reabsorption. Hypocalcemia activates to the receptor and increases PTH synthesis and urinary calcium reabsorption and ultimately in an increase in serum calcium. As for numerous GPCRs, mutations of the CaSR gene have been shown to cause mirror pathologies: activating and inhibiting mutations producing activation and loss of function of the receptor, respectively [25].

Autosomal dominant hypocalcemia results from a heterozygous activating mutation of the CaSR. It is to date the main genetic cause of

Table 16.2 Frequency of hypoparathyroidism etiologies

	Lund [46] 1980	Markowitz [47] 1982	Kruse [48] 1989	Halabe [49] 1994	Winer [42] 2003	Winer [43] 2008	Lienhardt[a] 2009
n	14	10 (Children)	29	17	27 (Adults)	14 (Children)	50 (Children)
CaSR					6 (22%)	1	19 (38%)
22q11				17			13 (26%)
APECED			1 (3%)		2 (7%)	5	7 (14%)
Postsurgery	9	1	2 (7%)	15	11 (41%)	1	1 (2%)
Idiopathic	4	7	26 (90%)	2	8 (30%)	7	7 (14%)
Other causes		2					2 (4%)

APECED autoimmune endocrinopathy–candidiasis–ectodermal dystrophy, *CaSR* calcium-sensing receptor
[a]Personal data

hypoparathyroidism (Table 16.2). Germ-line activating mutations of the CaSR increase the receptor sensitivity to circulating concentrations of ionized calcium in all target tissues and repress both the PTH synthesis and the urinary calcium reabsorption. The resultant hypocalcemia is most often fortuitously discovered in children or in adults. The biochemical phenotype is quite characteristic: hypocalcemia below 2 mM, normal or hyperphosphatemia; normal or high urinary calcium; normal or low PTH. The level of urinary calcium can drop in cases of severe and/or prolonged hypocalcemia: the existence of a low urinary calcium excretion does not therefore necessarily infer the hypothesis of an activating CaSR mutation. When a mutation is found in an index case, the measurement of the calcium level is sufficient for the genetic counseling. Autosomal dominant hypocalcemia can be diagnosed at any age of life and may present with various clinical symptoms, even within the same family. This absence of genotype–phenotype correlation suggests the importance of environmental factors already mentioned above [26]. One patient was described as having an activating homozygote mutation without presenting severe hypoparathyroidism [27]. It should be noted that some patients present with a pseudo-Bartter syndrome. In these patients, the CaSR activation induces not only an increase of the urinary calcium excretion but also a defect in sodium, potassium, and chlorine reabsorption, and a decrease of the transepithelial gradient [28, 29].

Hypoparathyroidism Due to Mutation Within the PTH Gene

Mutations in the PTH gene are extremely rare. Only three mutations have been described so far: two are autosomal recessive inheritance, and one is dominant. All are localized within the PTH coding region for the peptide precursor, the pre-proPTH, and disturb the maturing processing of PTH [30, 31].

Mitochondrial Diseases

The Kearns–Sayre syndrome is the most frequent manifestation of mitochondrial diseases associated with hypoparathyroidism. In 90% of cases, it is secondary to a large deletion of the mitochondrial DNA, but duplications have also been reported. Its transmission is maternal. The Kearns–Sayre syndrome is usually diagnosed during childhood but may also occur later on in adolescence or in early adulthood. The clinical manifestations are variable: impairments of the central (ataxia, mental retardation) or peripheral nervous system, ocular signs (ptosis, retinitis, ophthalmoplegia, and optic atrophy), myopathy, cardiac impairment (conduction disturbances, cardiomyopathy), neurosensorial deafness, endocrine disturbances (hypoparathyroidism, insufficient insulin secretion eventually leading to diabetes, hypogonadism, and hypomagnesemia), and renal tubulopathy. Endocrine impairments, notably hypoparathyroidism, are usually preceded by the neurological impairment. The deficiency in the PTH synthesis appears to be

secondary to the low mitochondrial energy production in the parathyroid cell, as this synthesis is very energy-costly [32]. MELAS syndrome and mitochondrial trifunctional protein (MTP) deficit can also be associated with hypoparathyroidism [33, 34].

Acquired Hypoparathyroidism

Hypoparathyroidism with Anti-CaSR Antibodies

Soon after the cloning of the CaSR gene, several teams suggested the possible existence of antibodies directed against the CaSR receptors. They subsequently identified a patient with acquired hypoparathyroidism [35]. Mayer et al. reported anti-CaSR antibodies in five out of 17 patients with isolated hypoparathyroidism, and in two out of 14 patients with hypoparathyroidism and polyendocrinopathy [36].

APECED Syndrome

APECED syndrome (autoimmune polyendocrinopathy candidiasis ectodermal dystrophy) is from a rare autosomal recessive pathology (1/80,000), manifesting early in childhood. Mutations have been found on both alleles of the *AIRE1* (autoimmune regulator) gene, which regulates the transcription of autoantibodies at the thymic level, in affected patients and families [37].

The patients progressively develop autoimmunity toward diverse organs, which include numerous endocrine glands [38]. This pathology evolves throughout life. Hypoparathyroidism is the most frequent symptom (80–95% of cases), often the first, and is due in 49% of cases to autoantibodies directed toward the NALP5 (NACHT leucine-rich-repeat protein 5) protein [39]. The identification of the anti-NALP5 antibody in patient sera could become the first-line diagnostic tool in suspected APECED, before any gene sequencing. To confirm the diagnosis, two out of three of the following clinical impairments are sufficient: chronic mucous–cutaneous candidosis, as soon as early childhood—hypoparathyroidism, with a peak of occurrence around 10 years of age—adrenal insufficiency, appearing around 15 years of age. The other clinical features appear throughout the patient's lifetime, including Graves' disease, autoimmune thyroiditis, active chronic hepatitis, alopecia, autoimmune anemia, malabsorption, vitiligo, insulin dependent diabetes, hypergonadotropic hypogonadism, bronchiolitis [40]—all of these symptoms being related to an organ-targeted autoimmunity. These patients require lifelong monitoring of these autoimmune pathologies.

Surgery

Any cervical, parathyroid, or thyroid surgery can cause hypoparathyroidism. This iatrogenic consequence (3–4% of interventions) essentially depends on the experience of the surgical team and the extension of the intervention. In fact, hypoparathyroidism has been found more frequently after thyroid surgery for invasive thyroid cancer, large multinodular goiters or Graves' disease. It is less frequent, and usually temporary, after surgery on a solitary parathyroid adenoma, or a subtotal parathyroidectomy. The stimulation of the remaining glandular tissue or of the reimplanted tissue prevents hypocalcemia. This cause of hypoparathyroidism is not very common in children [41].

Neonatal Hypoparathyroidism Secondary to Maternal Hyperparathyroidism

Hyperparathyroidism in pregnant women slows down the development of the fetal PTH synthesis as the fetus becomes hypercalcemic. At birth, there is a risk of acute neonatal hypocalcemia due to suppressed parathyroid gland function. This hypocalcemia resolves within a few weeks.

Frequency of Different Etiologies

There is no reliable study regarding the frequency of pediatric hypoparathyroidism etiologies—numerous cases being undiagnosed due to mild clinical expression (ADH) or to the recent

discovery of the other genes involved in the appearance of hypoparathyroidism, such as GCMB. We have undertaken in France, with physicians from the National Reference Centre for Rare Diseases of the Calcium and Phosphorus Metabolism, a retrospective study of patients affected with hypoparathyroidism, which outlines some epidemiological tendencies (Table 16.2). Based on this data, the molecular studies that we offer to patients affected with hypoparathyroidism are 22q, CaSR, PTH, and GCMB.

Differential Diagnosis

There are many causes of hypocalcemia besides what has been mentioned above:

- PTH resistance (genetic defect downstream to the PTH receptor) or chronic renal insufficiency—in these cases, PTH levels are elevated.
- Drugs: *Antiepileptic drugs* increase the vitamin D catabolism, *ketoconazole* inhibits the renal 1α-hydroxylase, prolonged use of *aluminum hydroxides* or of *calcium chelators*, such as citrate, and *laxatives*.
- Drugs used for the treatment of hypercalcemia, such as bisphosphonates, calcitonin, or chemotherapies.
- Miscellaneous:
  Acute pancreatitis—hypocalcemia results from the accumulation of calcium deposits in necrotic tissue.
  Hypomagnesemia, hypoalbuminemia.
  Septic shock and infectious syndrome.
- Causes of hyperphosphatemia.

Treatment

The conventional treatment will aim at correcting the hypocalcemia using 1-alpha hydroxylated vitamin D, through the forced intestinal absorption of calcium. The goals of the treatment may differ according to the clinical severity and etiology of the hypoparathyroidism [42].

Treatment and Monitoring

Diminished renal production of 1.25-$(OH)_2$D is the main cause of hypocalcemia in patients with hypoparathyroidism. Therefore, treatment with a 1α-hydroxylated vitamin D derivative (calcitriol or alfacalcidol) is the reference treatment. The dosage depends on the serum calcium and, above all, on urinary calcium excretion, which must be maintained within normal ranges to avoid urinary calcium intoxication and the development of lithiasis and/or nephrocalcinosis. We have established the following threshold in patients affected with hypoparathyroidism: 24 h-urinary calcium excretion below 5 mg/kg/d or urinary calcium/urinary creatinine <1 mmol/mmol (0.35 mg/mg) under the age of 5 years or <0.5 mmol/mmol (0.17 mg/mg) over the age of 5 years. Yearly renal ultrasonography is also recommended. The initial dose of 1α-hydroxylated vitamin D is 2–8 μg/day once or twice a day (1–4 μg/day of 1α/25-hydroxylated vitamin D twice per day) depending on the severity of the hypocalcemia. When the serum calcium reaches 2.2 mM or higher, the dosage is then reduced by 30–50%, to minimize the excreted urinary calcium levels and yet provide symptomatic relief. The lowest possible effective dose is often between 1 and 2 μg/day, but this has to be individually determined. This is a compromise between clinical symptomatology (prevention of seizures, absence of paresthesia, etc.) and prevention of nephrocalcinosis [43, 44].

We maintain in those children the 25 OH vitamin D in the normal range (above 40–50 nM or 16–20 ng/ml). This threshold should be upgraded in patients receiving antiepileptic drugs, which increase the risk of vitamin D deficiency, as well as in patients receiving recombinant PTH. In fact, in patients affected with hypoparathyroidism, the use of PTH will restore the renal 1 alpha hydroxylase activity and induce the hydroxylation of 25-(OH)D to 1.25-$(OH)_2$D.

Calcium supplementation is carried out intravenously during the acute phase of hypocalcemia and/or in case of high risk of seizures, until the serum calcium reaches approximately 2.2 mM. We recommend the dose of 1,000 mg/m^2 of body surface. The removal of the IV infusion always

induces a drop of 0.2 mM of the calcium level. An oral calcium supplementation should be considered as an adjuvant only. It is used at the start of the treatment until total restoration of the calcium pool (4–6 months), after which alimentary contribution (depending on the age) is sufficient. In France, daily dietary calcium needs are 500 mg/day up to 3 years, 700 mg/day up to 6 years, 900 mg/day up to 9 years, and 1,200 mg/day up to 19 years.

The off-label use of synthetic exogenous PTH (teriparatide) has shown its efficiency and is an interesting alternative in cases of hypoparathyroidism resistant to the conventional treatment. The dose for adults is about 30–40 μg/day via two subcutaneous injections [45]. We have recently reported doses of 5–15 μg/day given continuously with the aid of a pump in children, but this remains to be validated [46]. Osteosarcoma has been observed in rodent models at pharmacological doses greater than those used for humans [47]. Two reported cases of osteosarcoma in patients have been reported, but significance is not clear.

Monitoring of Specific Etiologies

In the case of *Autosomal Dominant Hypoparathyroidism*, iatrogenic complications such as increased urinary calcium excretion or nephrocalcinosis are frequent. Treatment must therefore be considered with caution and must only be used when calcium levels are lower than 1.80 mM, or when the symptoms are devastating. To avoid nephrocalcinosis, serum calcium is kept in the lower normal range while maintaining normal urinary calcium excretion. In rare cases, where this balance cannot be established, treatment by recombinant PTH has been proven effective [46, 48].

Patients affected with *APECED* may require higher doses of 1-hydroxylated vitamin D, as well as oral calcium supplementation, because of their digestive malabsorption. Alternatively, in these patients, worsening of the hypocalcaemia and/or elevated urinary calcium excretion may be due to an adrenal insufficiency. Moreover, antiepileptic drugs or liver diseases may inhibit the activity of the liver 25-hydroxylase. In this case, 1-hydroxylated vitamin D has to be replaced by 1.25-(OH)-2D if it is available. Finally, if the patients require an anticandidiasis treatment, it is necessary to closely monitor the serum calcium. Indeed, ketoconazole reduces the activity of several steroid P450-dependant cytochrome hydroxylases and may therefore induce a reduction in the concentration of 1.25-$(OH)_2$D.

For patients with hypoparathyroidism (DiGeorge syndrome in particular), *infectious episodes* may trigger acute hypocalcemia and seizures. Implementing a calcium perfusion during such episodes or temporarily increasing the dose of the 1-hydroxylated vitamin D derivatives may prevent incidents.

The genetic factors causing hypoparathyroidism have been discovered during the past few years. The main treatment is the 1α-hydroxylated vitamin D derivatives and oral calcium supplementation. In very rare cases, especially in cases of refractory hypoparathyroidism, the use of teriparatide, the recombinant PTH, is an interesting alternative.

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