Mini-review

Hypoparathyroidism in DiGeorge syndrome

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Summary

This brief review summarizes current knowledge concerning clinical characteristics of the hypoparathyroidism in DiGeorge syndrome (DGS) and pathogenetic hypotheses based upon studies in mouse models. Although a DiGeorge syndrome-like phenotype may be etiologically heterogeneous, most cases are caused by a genetic defect, i.e. an interstitial deletion of chromosome 22 named *del22q11*. We focus on patients with this genetic defect because a) within the population of patients with a DGS-like phenotype, this is the predominant group of patients, and b) both clinical and animal model studies have accumulated a wealth of information available for, and mostly inapplicable to, patients with DGS-like phenotype without *del22q11*.

KEY WORDS: hypoparathyroidism, DiGeorge syndrome.

Clinical features

Epidemiology

The most common underlying genetic defect, an interstitial, heterozygous deletion of chromosome 22, band q11.2 (here referred to as *del22q11*) is relatively frequent, in one study, the minimal incidence has been estimated at 1:7500 live births (1), an incidence of 1:4000 has also been suggested (2). Not all patients with *del22q11* are diagnosed with hypocalcemia. In a large survey of 340 patients with *del22q11*, 203 (60%) had been hypocalcemic, some of these (39%) had seizures (3) responsive to calcium supplements. Therefore, a simple calculation suggests that 1:12500 to 1:7000 live births is hypocalcemic because of *del22q11*. These patients do not necessarily have a fully fledged DiGeorge syndrome presentation, in fact, cases have been reported where hypoparathyroidism is the prominent clinical finding (4), although this is uncommon (5).

Clinical presentation

This is a classic hypoparathyroidism that generally manifests itself in the neonatal period. The diagnosis is based upon laboratory analyses that show reduced calcium ion, hyperfosphatemia, low parathormone (PTH). Intravenous infusion of PTH increases serum calcium as well as urinary and serum cyclic AMP levels. Treatment is also that of classic hypoparathyroidism (e.g. calcium and active vitamin D). It is important, however, to recognize the underlying disease in these patients because of the particular clinical history of the hypoparathyroidism in these patients (see below) but also because of other problems that *del22q11* patients often have and that need to be recognized as early as possible (e.g. hearing impairment, congenital heart disease, T-cell immune defects, etc). Clinical descriptions of the DGS/VCFS/del22q11 syndrome have been reviewed (2, 5-7). Briefly, there are three broad categories of clinical findings, "pharyngeal", neurobehavioral, and "others". The pharyngeal group of clinical findings refers to problems derived from developmental defects of the embryonic pharyngeal apparatus: congenital heart disease (aortic arch abnormalities and or conotruncal defects) craniofacial anomalies, external ear anomalies, velopharyngeal insufficiency, T-cell immune defects (from hypoplasia or aplasia of the thymus), hypocalcemia (from hypoplasia or aplasia of the parathyroids). The neurobehavioral phenotype includes learning disabilities and psychiatric disorders. The "others" category includes miscellaneous findings like vascular anomalies, skeletal anomalies, kidney anomalies, and other less common findings.
As for most of the clinical findings associated with *del22q11*, hypoparathyroidism may or may not be present, and if it is present may be of different clinical severity (8). Hypocalcemia may present itself as the first dramatic clinical sign of the syndrome in the neonate (9-12), and if the patient does not have congenital heart disease (as it happens in 20-30% of *del22q11* patients) or severe craniofacial abnormalities (which are not common), the syndromic diagnosis may be very difficult at this age. At the other end of the spectrum, the patient may not have any hypocalcemic episode, but there may be a latent hypoparathyroidism, i.e. revealed only by hypocalcemic challenge (13, 14).

Clinical history

Generally, *del22q11* patients with hypoparathyroidism have episodes of hypocalcemia in early life with resolution within the first year of life. In one study, long term treatment was necessary in 10 out of 40 patients (11). Stress or increased natural requirement of calcium (e.g. during adolescence or pregnancy) may trigger recurrence of hypocalcemic episodes or unmask latent hypoparathyroidism (12, 15). Latent hypoparathyroidism may be revealed in these patients by infusion of ethylendiaminotetracetic acid (16, 17). There are not enough data in the literature to comment on how common latent or recurrence of hypoparathyroidism is among *del22q11* patients.
Analysis of genetically engineered mouse models (described below) provides a rationale for recurrence or latency of hypoparathyroidism. Indeed, the genetic defect causes a reduction of expression of the gene encoding PTH, most likely due to the reduced number of cells expressing the gene. Therefore, the capacity of PTH production is reduced, perhaps sufficient in "normal" conditions, but may become insufficient if the demand for PTH increases.

Etiopathogenesis

Development

DiGeorge syndrome derives from a developmental defect of the pharyngeal apparatus. This is a transient embryonic system, present only in vertebrates, composed tissue bulges (pharyngeal arches) separated by epithelial invaginations (pharyngeal pouches) (6). The parathyroids and the thymus develop from the endoderm of the third pharyngeal pouch. A number of genes required for the formation or development of the third pouch (e.g. *Hoxa3, Pax1, Tbx1* and others) are also required for the development of both parathyroids and thymus (review in ref. 18). One of the first parathyroid-specific markers to appear is the transcription factor Gcm2, shortly followed by the expression of PTH. *Gcm2* mutation eliminates the parathyroids but does not affect the thymus (19). Interestingly, the elimination of the parathyroid glands is not sufficient to eliminate the production of PTH as it can also be produced by thymic cells (19). These considerations suggest that the hypoparathyroidism in DiGeorge syndrome is more likely to derive from developmental problems of the pharyngeal pouches than from specific defects of the parathyroids.

Genetics

The chromosomal deletion *del22q11* eliminates a copy of over 30 genes, making it difficult to establish which gene (or genes) is responsible for the hypoparathyroidism. Extensive genetic manipulation of the mouse genome, however, has provided substantial amount of information on this issue. The first mouse model of *del22q11* was produced by deleting a mouse chromosomal segment homologous to that deleted in *del22q11*. Mice carrying this deletion had heart defects similar to those found in *del22q11* patients but did not have hypocalcemia or reduced PTH serum levels (20). However, further analysis of these mice demonstrated a strongly reduced level of expression of the PTH gene in the developing parathyroids (21), providing evidence that a gene within the mouse deleted region is a likely candidate for the hypoparathyroidism in DiGeorge syndrome. Further genetic analyses identified *Tbx1*, a gene included in the mouse and human deletion, as a gene necessary for the formation of thymus and parathyroids as well as other structures derived from the pharyngeal apparatus (22, 23). *Tbx1* heterozygous mutant mouse embryos have reduced expression of the *Pth* gene (Fig. 1A-B) just like mice with a chromosomal deletion modeling *del22q11* (21). Hence, *Tbx1* is a dosage sensitive gene that when homozygously deleted prevents the formation of the parathyroids, and when heterozygously deleted causes reduced PTH gene expression and reduced parathyroid size. The role of *Tbx1* in human hypoparathyroidism has recently been confirmed with the report of patients with *Tbx1* mutations associated with a DiGeorge syndrome phenotype, including hypoparathyroidism (24). Hence, *Tbx1* haploinsufficiency is sufficient to cause hypoparathyroidism in humans.

How *Tbx1* functions in parathyroid development is still unclear. It is clear, however, that *Tbx1* mutation profoundly affects the segmentation of the pharyngeal apparatus, eliminates the 3rd and 4th pharyngeal pouches, and strongly reduces the number of pharyngeal endodermal cells (23, 25). Hence, the most likely scenario is that *Tbx1* affects parathyroids development because it affects the specification or proliferation of the endodermal precursors of PTH-expressing cells, which also express *Tbx1*. An indirect support for this model is the demonstration that tissue-specific ablation of *Tbx1* in the mesoderm does not affect the formation of the third pharyngeal pouch (26) suggesting a cell-autonomous function in endodermal cells. Further analysis of *Tbx1* function during parathyroid development is necessary to confirm a cell-autonomous function in the endodermal precursors of the parathyroids, and to test whether *Tbx1* has a role in this gland also after formation. Current models do not allow to test these hypotheses.

Tbx1 may not be the only gene in the *del22q11* important for parathyroid development. Mouse mutants for the CRKL gene,

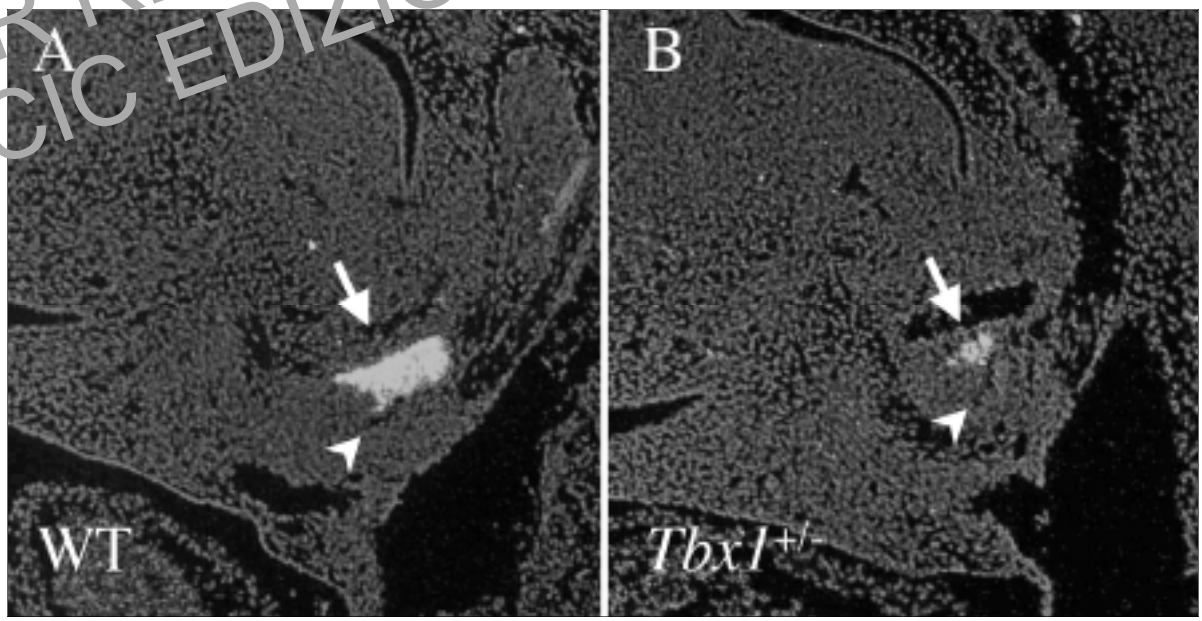

Figure 1 - In situ hybridization of sagittal sections from mouse embryos at embryonic day 11.5 using a probe identifying the PTH gene transcript. The hybridization signal is shown in red (arrows). A) Wild type (WT) embryo. B) *Tbx1+/–* embryo. Note the strong reduction of the hybridization signal, most likely due to reduced number of PTH-expressing, endodermally derived cells. Arrowheads indicate the third pharyngeal pouch.

another gene included in the *del22q11* region, also have thymic and parathyroid defects prospecting the interesting possibility that two genes may play a role in the human phenotype (27). However, to date no mutations of this gene have been reported in patients with DiGeorge syndrome phenotype.

Conclusions

Hypoparathyroidism in *del22q11*/DiGeorge syndrome may be the earliest, and sometimes dramatic, clinical manifestation of the disease. Although symptoms may disappear within the first year of life, recurrence is possible. Conversely, *del22q11* patients may carry latent hypoparathyroidism that may be unmasked later in life. Therefore, patients with *del22q11* should be monitored for parathyroid function throughout their lives. The role of the *Tbx1* as the causative gene for hypoparathyroidism is established, although contribution of other genes, such as CRKL, cannot be ruled out. Mouse mutant model analyses show a reduction of PTH-expressing tissue in heterozygous and complete absence of parathyroids in the homozygous mutants. This phenotype suggests a role of *Tbx1* in the specification and or expansion of endodermally-derived precursors of endocrine parathyroid cells.

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