Endocrine (2011) 40:325–331
DOI 10.1007/s12020-011-9516-8

ORIGINAL ARTICLE

Case seminar: a young female with acute hyponatremia and a sellar mass

Sandra Pekic · Mirjana Doknic · Dragana Miljic · Alexandru Saveanu · Rachel Reynaud · Anne Barlier · Thierry Brue · Vera Popovic

Received: 21 February 2011 / Accepted: 27 July 2011 / Published online: 24 August 2011

Abstract In familial cases of combined pituitary hormone deficiency the most common mutations are that of Prophet of Pit 1 (PROP1) gene. PROP1 mutations are associated with deficiencies of growth hormone, thyrotropin, prolactin, and gonadotropins (follicle-stimulating hormone and luteinizing hormone), with evolving adrenocorticotropin (ACTH) deficiency in some cases. On imaging in most patients the pituitary gland is hypoplastic, but occasionally transient pituitary enlargement is found. We report a 22-year-old female initially diagnosed at age 12 with familial hypopituitarism due to PROP1 mutation, who presented with coma and respiratory arrest (acute hyponatremia). She was urgently treated in Intensive Care Unit of Emergency Center with hypertonic saline and stress doses of hydrocortisone, which resulted in the fast increase of plasma osmolality resulting in the osmotic demyelination syndrome. Simultaneously and incidentally on computed tomography scan a large sellar and suprasellar mass were reported as possible Rathke's cleft cyst or craniopharyngioma. Once the patient was stable, ACTH deficiency was documented. She remained replaced with hydrocortisone and subsequently underwent transphenoidal surgery. The removed sellar content revealed no pituitary adenoma or pituitary cells, but only an eosinophilic, colloid-like mass, and necrotic acellular debris. Her sister with hypopituitarism had an empty sella. Genetic testing in both sisters revealed the same homozygous c.150delA mutation in PROP1 gene. Here we report two sisters with the same PROP1 mutation who presented in adulthood with different pituitary morphology, one of them with a large sellar and suprasellar mass, in which transphenoidal surgery provided an extremely rare opportunity for a histopathological analysis of the sellar content. Due to the lack of endocrine care during the transition period hypocortisolism which evolved, a consequence of PROP1 mutation, was not recognized. Empirical use of hydrocortisone in the Intensive Care in our patient with life-threatening acute hyponatremia was appropriate but because glucocorticoid therapy on its own corrects hyponatremia even after stopping hypertonic saline infusion, the risk for over-correction of hyponatremia in ACTH deficiency is high.

Keywords PROP1 mutation · Hypopituitarism · Hypocorticism · Hyponatremia · Sellar mass

S. Pekic · M. Doknic · D. Miljic · V. Popovic (✉)
Clinic of Endocrinology, Clinical Center Serbia, Belgrade, Serbia
e-mail: popver@eunet.rs

S. Pekic · M. Doknic · V. Popovic
Faculty of Medicine, University of Belgrade, Belgrade, Serbia

A. Saveanu · R. Reynaud · A. Barlier · T. Brue
Department of Endocrinology and Reference Centre for Rare Pituitary Diseases, Centre Hospitalo-Universitaire Timone, Marseille, France

A. Saveanu · A. Barlier
Laboratory of Biochemistry and Molecular Biology, Centre Hospitalo-Universitaire Conception, Assistance Publique Hôpitaux de Marseille and Université de La Méditerranée, Marseille, France

Introduction

Prophet of Pit 1 (PROP1) is a pituitary-specific transcriptional factor expressed during the development of the pituitary gland [1–4]. Mutations in PROP1 are the most commonly identified genetic cause of multiple pituitary hormone deficiencies (growth hormone (GH), thyrotropin (TSH), prolactin (PRL), and gonadotropin deficiencies, in

some cases with evolving adrenocorticotropin (ACTH) deficiency; [5–9]). The phenotype associated with PROP1 mutations is highly variable both within and between pedigrees concerning the severity of the disease, the time of onset of pituitary hormone deficiencies, ACTH reserve, magnetic resonance imaging (MRI) findings or final height [7, 10–13]. This is illustrated in the present report with different hormonal and pituitary morphology phenotypes in two sisters. In most patients with PROP1 mutation the pituitary gland is normal or hypoplastic, or rarely transitory hyperplastic during childhood. We describe a young female with PROP1 mutation, large sellar and suprasellar mass mimicking a tumor, with previously undiagnosed central hypocortisolism which evolved due to PROP1 mutation. In early adulthood this undiagnosed central hypocortisolism manifested with acute, life-threatening, hyponatremia. Both acute hyponatremia and sellar mass posed diagnostic and therapeutic problems.

Case report

A female patient, now aged 22 years (body height 160 cm, weight 38–42 kg), was investigated and treated by a pediatric endocrinologist for short stature at age 12 years and her older sister at age 16. Both sisters were born at term after uneventful pregnancies, with normal birth weights and lengths. Neonatal signs of GH deficiency (hypoglycemia, prolonged jaundice, and convulsions) were not reported. Growth retardation in both sisters was noticed at age 6–7 and they were referred to pediatric endocrinologist at age 12 and 16, respectively. Two other sisters were healthy, with normal height. GH deficiency and central hypothyroidism in both sisters were diagnosed by pediatrician according to poor GH response to clonidine test (peak 1 mIU/l), low T4 level (less than 20 nmol/l), low TSH level (1 mIU/l) and they were replaced with recombinant human GH (rhGH) and L-thyroxine. They were treated with GH until age 18. Sex steroids were then introduced. Insulin tolerance test (ITT) was performed in our patient at age 16 with baseline cortisol 250 nmol/l and peak cortisol of 400 nmol/l. This was then considered to be adequate and she was not replaced with hydrocortisone. PRL level was low (40 mU/l). Genetic testings for hypopituitarism were not performed. During the transition period both our patient and her sister felt well (age 18–21) and were not under endocrine surveillance.

At age 21, the index patient felt tired, lost appetite and body weight (9 kg within 5 months), and began vomiting. She was admitted to a local hospital and was treated with 500 ml of 5% glucose upon which she became comatosed and was urgently transferred to an Intensive Care Unit of an Emergency Center. She was comatose without spontaneous respiration, was artificially ventilated, and laboratory analysis showed severe hyponatremia (98 mmol/l). Her free T4 level was normal (15 ng/l). Hyponatremia was rapidly corrected (from 98 to 128 mmol/l over the first 24 h) with administration of hypertonic sodium which was then stopped after which stress doses of hydrocortisone were given and sodium reached 136 mmol/l over the 48 h. Due to sodium over-correction she subsequently developed symptoms of the osmotic demyelination syndrome (ODS) with paraparesis. ODS symptoms started immediately after sodium correction. Incidentally on computed tomography (CT) scan of the brain an intrasellar mass with suprasellar extension was detected, reported by the radiologist as possible craniopharyngioma or Rathke's cleft cyst (Fig. 1). After stabilizing her condition and partial recovery of ODS, ACTH deficiency was diagnosed (morning cortisol 110 nmol/l, ACTH undetectable) and she was replaced with hydrocortisone. Two months later transphenoidal operation was performed and a gelatinous mass was evacuated from the sella. Histopathology examination of formalin-fixed and paraffin-embedded tissue was performed and hematoxylin and eosin (H-E) staining revealed no pituitary adenoma or pituitary cells. Only an eosinophilic, colloid-like mass, necrotic acellular debris and some focal erythrocytes were detected (Fig. 2). The patient's condition gradually improved and she fully

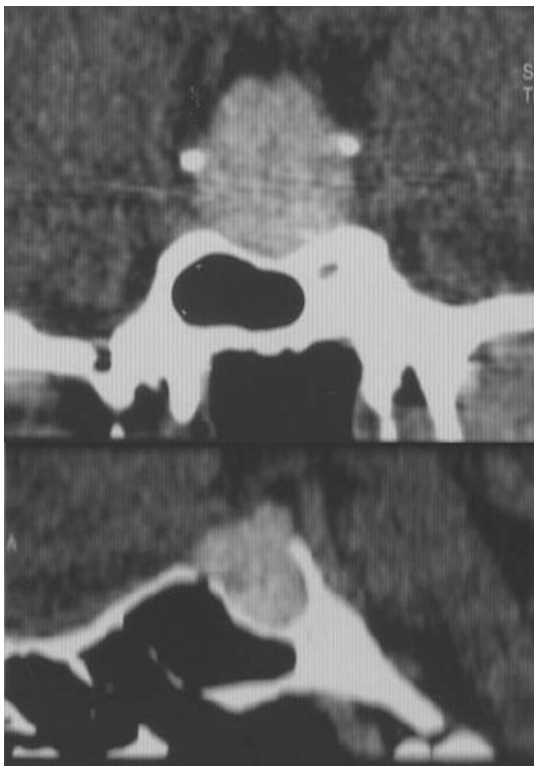

Fig. 1 Coronal and sagital CT scans of the brain before the transphenoidal operation showing intrasellar and suprasellar mass lesion

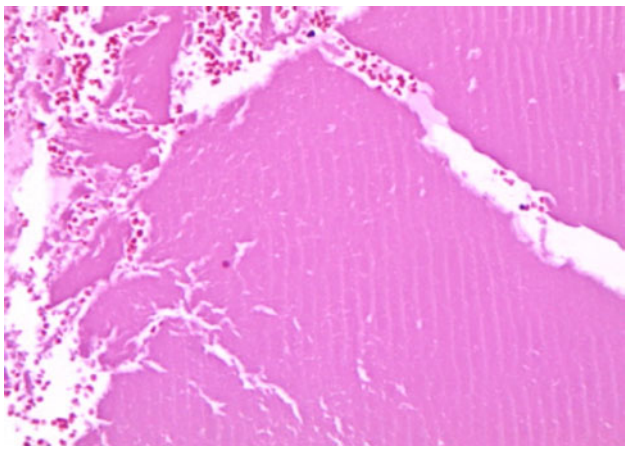

Fig. 2 The sellar contents obtained during the transphenoidal operation consisted of eosinophilic, colloid-like mass and necrotic acellular debris (H&E ×250)

recovered neurologically. MRI scan of the pituitary region 3 months after operation showed a residual cystic mass in the sella (Fig. 3). She continued pituitary replacement therapy and is under adult endocrine care.

Recently, MRI of the sellar region in the older sister showed empty sella, with preserved pituitary stalk and a hypoplastic pituitary gland (Fig. 4). Endocrine evaluation showed that baseline morning cortisol was intermediate (250 nmol/l). Testing confirmed insufficient cortisol response and she was also replaced with hydrocortisone. Her FT4 level (on Levo-thyroxine therapy) was normal (18 ng/l), PRL level was low (32 mIU/l), IGF-1 level was low (25 ng/ml) and she was replaced with sex steroids.

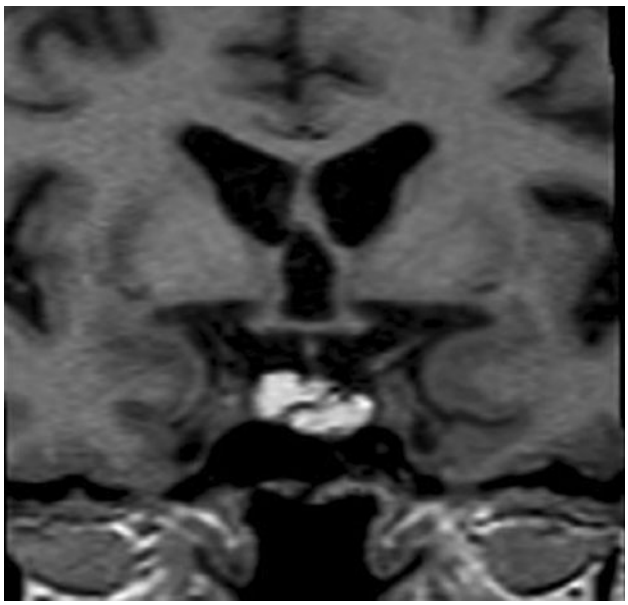

Fig. 3 Coronal MRI scan of the sellar region 3 months after transphenoidal operation showing remnant of the cystic mass

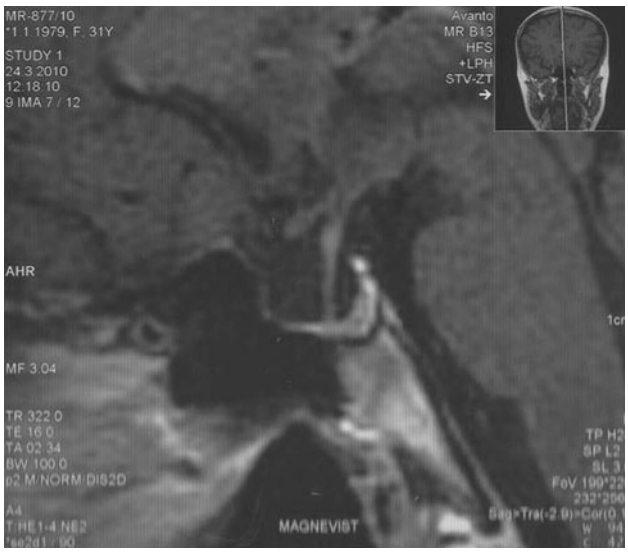

Fig. 4 Coronal MRI scan of the sellar region of the older sister of our patient showing and empty sella with hypoplastic pituitary gland and preserved pituitary stalk

Genetic analysis of the PROP1 gene in both sisters and their mother was performed in the Laboratoire de Biologie Moleculaire, Hopital de la Conception, Marseille, France through the Genhypopit network [14] and demonstrated that both sisters had a homozygous c.150delA mutation in the exon 2 of PROP1 gene while their mother was heterozygous for this single nucleotide deletion.

Discussion

In summary, here we describe a 22-year-old female with familial combined pituitary hormone deficiency due to PROP1 mutation (c.150delA), who presented with a large sellar and suprasellar mass, developed ACTH deficiency which was not recognized during the transition period because she felt well (from 18 to 21 years of age) and was not under endocrine care. This resulted in severe and potentially lethal clinical condition (coma with respiratory arrest due to acute hyponatremia) in early adulthood which was difficult to manage.

Familial hypopituitarism due to PROP1 mutation and evolving central hypocortisolism

Two sisters harbored the same mutation and despite a similar genetic background, presented with different pituitary morphology one with hypoplastic pituitary and the other with a large pituitary mass. In our family, as in other patients with PROP1 mutation, GH and TSH deficiency are commonly recognized in childhood [15].These patients generally lack perinatal signs of hypopituitarism and have

normal birth lengths, but progressive growth failure develops later in childhood. The diagnosis is usually made at age 6–7 [16, 17]. There are patients with PROP1 mutation who grow well, and reach normal final stature despite profound GH deficiency [10–12, 18]. Also, there are cases with PROP1 mutation in whom the initial presentation is isolated hypogonadotropic hypogonadism [19]. Evolving ACTH deficiency has been described in some PROP1 patients [13, 18, 20–23]. When evaluated at age 16 our patient had a normal cortisol response to insulin induced hypoglycemia. Since our patient was not reevaluated after transition period symptoms such as fatigue, weight loss, and dizziness were not recognized as clinical signs of central adrenal insufficiency. This resulted in severe, life-threatening acute hyponatremia upon administration of fluids. Cortisol deficiency is absent or develops later in some patients with PROP1 mutation, suggesting a different mechanism for this deficiency. In the study of Bottner et al., all nine patients with PROP1 mutation developed at least partial ACTH insufficiency, with a gradual decline of the pituitary adrenal axis function and eventually required replacement with hydrocortisone at a mean age of 18 years [23]. It is possible that a progressive apoptosis of the corticotroph cells and/or decreased ACTH secretion occurs with age because of the lack of important signals from the other pituitary cell lineages, absent in the pituitary gland of these patients. PROP1 has some role in differentiation or viability of corticotroph cells. It is demonstrated that PROP1 expression is not completely switched off during embryonic development and persists in adult pituitary [24]. Adrenal insufficiency occurs after other anterior pituitary axes deficiencies. In some patients, accumulation of fibrous material in the dysmorphic pituitary gland with formation of pituitary mass, may affect the viability of residual functional cells. For the clinician, it is important to monitor adrenal function regularly (baseline morning cortisol, ITT, and ACTH stimulation test) because these patients are at risk for developing later central adrenal failure. This is one of the reasons why early genotyping is directly helpful to the management of patients with congenital familial forms of combined hypopituitarism since patients with other mutations, for instance POU1F1 mutations, are not at risk for developing corticotroph deficiency or a pituitary mass [16].

Sellar masses in familial hypopituitarism

On imaging our patient presented with sellar mass with suprasellar extension. Differential diagnosis of sellar mass in a young patient with hypopituitarism includes a variety of diseases: pituitary and non-pituitary tumors, pituitary hyperplasia, cystic lesions, lymphocytic hypophysitis, vascular lesions (aneurysm), inflammatory, infective lesions, and metastasis of malignant tumors [25, 26]. In our patient, radiologist's report suggested possible craniopharyngioma or Rathke's cleft cyst. Most patients with familial hypopituitarism and PROP1 mutation have a hypoplastic anterior pituitary gland with preserved pituitary stalk and normal posterior pituitary gland [8, 18, 27]. There are indeed some patients with PROP1 mutations who present with enlarged pituitary fossa and transient pituitary hyperplasia [19, 23, 27–33]. In these patients it has been described that the sellar mass can wax and wane in size before involution [20]. The reason for the changing pituitary size during life is not known. Since our patient had a large cystic mass with suprasellar extension she was operated. There are only two reports (one is an abstract) of patients with PROP1 mutation who were operated because of the sellar mass lesion [33]. The histopathology of a surgically removed pituitary mass from a first operated PROP1 deficient Jamaican patient revealed no recognizable cell line but amorphous material, as in our patient. Another two operated patients were two children with PROP1 mutation from Poland [33]. Histological assessment of the removed tissue revealed epithelial cells forming gland-like microcystic structures, most of them filled with eosinophilic colloid and the presence of all hormonal phenotypes of cells. An enlarged pituitary gland presenting with hyperintense signal at MRI could reflect an elevated protein content and correspond to the same amorphous material described in our patient and in the previously reported patient from Jamaica. These findings suggest that pituitary enlargement may represent cystic hyperplasia of the intermediate pituitary lobe. Voutetakis et al. reported pituitary MRI in 15 patients with PROP1 gene mutations of whom 5 patients had pituitary enlargement and suggested that the mass causing the pituitary enlargement most likely originated from the intermediate lobe [28]. This enlargement might result from abnormal development of the anterior lobe and the absence of physiologic regression of the intermediate pituitary lobe during organogenesis, as was demonstrated by Ward et al. in Ames dwarf mice [34]. Interestingly, while in the published cases sellar masses in patients with PROP1 mutations were seen predominantly in early childhood [20, 30, 31] with subsequent shrinkage of the pituitary mass between age 10 and 20, our patient had a large sellar mass detected in adulthood which needed operation.

Hyponatremia in a patient with a CNS mass

Hyponatremia, defined as a serum sodium concentration below 135 mmol/l, is one of the most frequently encountered electrolyte disorders in clinical practice. This disorder

of water and sodium homeostasis is a very common problem in patients with CNS masses [35, 36], as well as in patients with significant cardiac, hepatic, or renal dysfunction, postoperative patients, older patients on thiazide diuretics, patients with malignancies or psychiatric illness, endurance athletes, or drugs targeting central nervous system: antipsychotic drugs (fluphenazine, thiothixene, and phenothiazine), antidepressants (amitriptyline, selective serotonin reuptake inhibitors: fluoxetine, fluvoxamine, paroxetine, and sertraline) and anticonvulsants (carbamazepine). Hyponatremia is most often caused by inappropriately elevated plasma levels of the antidiuretic hormone arginine vasopressin (AVP), labeled as the syndrome of inappropriate antidiuretic hormone (SIADH), which is caused by continued secretion of AVP despite plasma hypotonicity, leading to water retention and a dilutional decrease in serum sodium levels [37]. One of the known causes of hyponatremia is hypocorticism (as in our patient). Both primary and secondary adrenal deficiency can cause hyponatremia, but the mechanisms by which they do so are different. Primary adrenal deficiency leads to salt-wasting from mineralocorticoid deficiency, with resulting ECF volume contraction, hypovolemia, and hypotension. In contrast, patients with ACTH deficiency do not develop ECF volume contraction, since they maintain adequate aldosterone secretion which prevents renal sodium wasting. Hyponatremia in ACTH deficiency is due to water retention as a result of inappropriately elevated AVP levels. Elevated plasma AVP levels have clearly been documented in animals and patients with hypopituitarism [38, 39]. Most patients with central hypocortisolism manifest chronic hyponatremia, but occasionally patients can present with life-threatening cerebral edema due to acute hyponatremia, which was how our patient presented. This was probably due to the hypotonic infusions that she received upon admission to a local hospital. Although we do not have documentation of chronic hyponatremia in this patient, it seems likely that some of her symptoms in the months before presentation (e.g., weight loss, nausea, vomiting, fatigue, instability, irritability, and change in cognitive functioning) were likely to be due to chronic hyponatremia.

Management of hyponatremia

Treatment options for acute hyponatremia are fluid restriction and hypertonic saline. The clinician should try to ascertain when hyponatremia started, and how long was it present, before correcting it but this might not be always possible as was in our patient. Our patient clearly presented with acute hyponatremia (coma and respiratory arrest) in whom correction with hypertonic saline in the first 24 h followed by stress doses of hydrocortisone the next 24 h resulted in over-correction of sodium and as a consequence ODS. In patients in whom process of brain adaptation to hyponatremia has had time to occur, treatment of hyponatremia with hypertonic fluids can raise the plasma osmolality too fast leading to excessive loss of intracellular water, cell shrinkage, and the ODS [40]. It is recommended that patients with serious signs or symptoms of hyponatremia should receive hypertonic saline at a rate of about 1 ml/kg/h for the first several hours, raising the serum sodium concentration usually by 10–12 mmol/day during the first 24 h of treatment and by less than 18 mmol/l over 48 h [36]. Serum sodium levels should be checked every 1 to 2 h. However, treatment of hypocortisolism-induced hyponatremia can be more difficult, because glucocorticoid replacement leads to a marked free water excretion, or aquaresis, which continues correction of the hyponatremia even after hypertonic saline infusion has been stopped which was the case in our patient [41]. Appropriate therapy of such patients includes administering water, either orally or intravenously as 5% dextrose, to replace ongoing urine losses, and/or administration of desmopressin to shut off the aquaresis and slow the correction of the osmolality [42].

Conclusion

This is a well documented case of PROP1 mutation in two sisters, with familial combined pituitary hormone deficiencies, of whom one had evolving unrecognized central hypocorticism with a large sellar and suprasellar mass on imaging, which after operation proved to be acellular colloid. This provided an extremely rare opportunity for a histopathological analysis of the sellar content in congenital hypopituitarism caused by PROP1 mutation. The other sister on imaging presented with empty sella. The clinical significance of this presentation is that genotyping patients with familial hypopituitarism raises the awareness for the risk of evolving adrenal failure and of pituitary mass. If PROP 1 mutation had been known, our patient could have avoided life-threatening hyponatremia and complications of its management. Fortunately, the patient recovered neurologically and is well.

Acknowledgments The authors thank Professor Dr. Joseph G. Verbalis, Georgetown University Medical Center, Washington, DC for his substantial and important contribution in discussing the clinical course and management of hyponatremia in our patient. Genetic analysis of the PROP1 gene in both sisters and mother was performed in the Laboratoire de Biologie Moleculaire, Hopital de la Conception, Marseille, France (Prof. Alain Enjalbert). This investigation was supported by a grant from the Ministry of Science of Republic of Serbia (Project 175033) and a grant from the French National Research Agency (ANR-08-GENO-026-01).

Conflict of interest The authors have nothing to disclose.

References

1. J.S. Dasen, J.P. Barbera, T.S. Herman, S.O. Connell, L. Olson, B. Ju, J. Tollkuhn, S.H. Baek, D.W. Rose, M.G. Rosenfeld, Temporal regulation of a paired-like homeodomain repressor/TLE corepressor complex and a related activator is required for pituitary organogenesis. Genes Dev. **15**, 3193–3207 (2001)
2. M.W. Sornson, W. Wu, J.S. Dasen, S.E. Flynn, D.J. Norman, S.M. O'Connell, I. Gukovsky, C. Carrière, A.K. Ryan, A.P. Miller, L. Zuo, A.S. Gleiberman, B. Andersen, W.G. Beamer, M.G. Rosenfeld, Pituitary lineage determination by the Prophet of Pit-1 homeodomain factor defective in Ames dwarfism. Nature **384**, 327–333 (1996)
3. P.J. Gage, M.L. Brinkmeier, L.M. Scarlett, L.T. Knapp, S.A. Camper, K.A.L. Mahon, The Ames dwarf gene, df, is required early in pituitary ontogeny for the extinction of Rpx transcription and initiation of lineage-specific cell proliferation. Mol. Endocrinol. **10**, 1570–1581 (1996)
4. L.E. Cohen, Genetic regulation of the embryology of the pituitary gland and somatotrophs. Endocrine **12**, 99–106 (2000)
5. M.T. Dattani, I.C. Robinson, The molecular basis for developmental disorders of the pituitary gland in man. Clin. Genet. **57**, 337–346 (2000)
6. S. Mody, M. Brown, J.S. Parks, The spectrum of hypopituitarism caused by PROP1 mutations. Best Pract. Res. Clin. Endocrinol. Metab. **16**, 421–431 (2002)
7. M.T. Dattani, Growth hormone deficiency and combined pituitary hormone deficiency: does the genotype matter? Clin. Endocrinol. **63**, 121–130 (2005)
8. W. Wu, J.P. Cogan, R.W. Pfaffle, J.S. Dasen, H. Frisch, S.M. O′Connell, S.E. Flynn, M.R. Brown, P.E. Mullis, J.S. Parks, J.A. Phillips 3rd, M.G. Rosenfeld, Mutation in PROP1 cause familial combined pituitary hormone deficiency. Nat. Genet. **18**, 147–149 (1998)
9. A.L. Rosenbloom, A.S. Almonte, M.R. Brown, D.A. Fisher, L. Baumbach, J.S. Parks, Clinical and biochemical phenotype of familial anterior hypopituitarism from mutation of the PROP1 gene. J. Clin. Endocrinol. Metab. **84**, 50–57 (1999)
10. A. Arroyo, F. Pernasetti, V.V. Vasilyev, P. Amato, S.S.C. Yen, P.L. Mellon, A unique case of combined pituitary hormone deficiency caused by a PROP1 gene mutation (R120C) associated with normal height and absent puberty. Clin. Endocrinol. **57**, 283–291 (2002)
11. M. Doknic, S. Pekic, M. Djurovic, V. Zivkovic, V. Popovic, Multiple pituitary hormone deficiency (MPHD) associated with normal height, absent puberty and obesity. Pediatr. Endocrinol. Rev. **1**, 32–33 (2004)
12. M.T. Dattani, GH deficiency might be associated with normal height in PROP1 deficiency. Clin. Endocrinol. **57**, 157–158 (2002)
13. T.C. Vieira, M.R. da Silva, J. Abucham, The natural history of the R120C PROP1 mutation reveals a wide phenotypic variability in two untreated adult brothers with combined pituitary hormone deficiency. Endocrine **30**, 365–369 (2006)
14. R. Reynaud, M. Gueydan, A. Saveanu, S. Vallette-Kasic, A. Enjalbert, T. Brue, A. Barlier, Genetic screening of combined pituitary hormone deficiency: experience in 195 patients. J. Clin. Endocrinol. Metab. **91**, 3329–3336 (2006)
15. R. Reynaud, M. Chadli-Chaieb, S. Vallette-Kasic, A. Barlier, J. Sarles, I. Pellegrini-Bouiller, A. Enjalbert, L. Chaieb, T. Brue, A familial form of congenital hypopituitarism due to a *PROP1* mutation in a large kindred: phenotypic and in vitro functional studies. J. Clin. Endocrinol. Metab. **89**, 5779–5786 (2004)
16. J.S. Parks, M.R. Brown, D.L. Hurley, C.J. Phelps, M.P. Wajnrajch, Heritable disorders of pituitary development. J. Clin. Endocrinol. Metab. **84**, 4362–4370 (1999)
17. J. Deladoey, C. Fluck, A. Buyukgebiz, B.V. Kuhlmann, A. Eble, P.C. Hidnmarsh, W. Wu, P.E. Mullis, "Hot spot" in the PROP1 gene responsible for combined pituitary hormone deficiency. J. Clin. Endocrinol. Metab. **84**, 1645–1650 (1999)
18. S. Vallette-Kasic, A. Barlier, C. Teinturier, A. Diaz, M. Manavela, F. Berthezene, P. Bouchard, J.L. Chaussain, R. Brauner, I. Pellegrini-Bouiloler, P. Jaquet, A. Enjalbert, T. Brue, PROP1 gene screening in patients with multiple pituitary hormone deficiency reveals two sites of hypermutability and a high incidence of corticotroph deficiency. J. Clin. Endocrinol. Metab. **86**, 4529–4535 (2001)
19. R. Reynaud, A. Barlier, S. Vallette-Kasic, A. Saveanu, M.P. Guillet, G. Simonin, A. Enjalbert, P. Valensi, T. Brue, An uncommon phenotype with familial central hypogonadism caused by a novel PROP1 gene mutant truncated in the transactivation domain. J. Clin. Endocrinol. Metab. **90**, 4880–4887 (2005)
20. B.B. Mendonca, M.G.F. Osorio, A.C. Latronico, V. Estefan, L. Su Sih Lo, I. Arnhold, Longitudinal hormonal and pituitary imaging changes in two females with combined pituitary hormone deficiency due to deletion of A301,G302 in the PROP1 gene. J. Clin. Endocrinol. Metab. **84**, 942–945 (1999)
21. G. Agarwal, V. Bhatia, S. Cook, P.Q. Thomas, Adrenocorticotropin deficiency in combined pituitary hormone deficiency patients homozygous for a novel PROP1 deletion. J. Clin. Endocrinol. Metab. **85**, 4556–4561 (2000)
22. F. Pernasetti, S.P.A. Toledo, V.V. Vasilyev, C.Y. Hayashida, J.D. Cogan, C. Ferrari, D.M. Lourenco, P.L. Mellon, Impaired adrenocorticotropin-adrenal axis in combined pituitary hormone deficiency caused by a two-base pair deletion (301-302delAG) in the Prophet of Pit-1 gene. J. Clin. Endocrinol. Metab. **85**, 390–397 (2000)
23. A. Bottner, E. Keller, J. Kratzsch, H. Stobbe, J.F.W. Weigel, A. Keller, W. Hirsch, W. Kiess, W.F. Blum, R.W. Pfaffle, *PROP1* mutations cause progressive deterioration of anterior pituitary function including adrenal insufficiency: a longitudinal analysis. J. Clin. Endocrinol. Metab. **89**, 5256–5265 (2004)
24. S. Nakamura, A. Ohtsuru, N. Takamura, G. Kitange, Y. Toukunaga, A. Yasunaga, S. Shibata, S. Yamashita, Prop-1 gene expression in human pituitary tumors. J. Clin. Endocrinol. Metab. **84**, 2581–2584 (1999)
25. K. Thapar, K. Kovacs, B.W. Scheitauer, M.O. Lloyd (eds.), *Diagnosis and management of pituitary tumors* (Humana press, Totowa, 2001)
26. R. Carpinteri, I. Patelli, F.F. Casanueva, A. Giustina, Pituitary tumours: inflammatory and granulomatous expansive lesions of the pituitary. Best Pract. Res. Clin. Endocrinol. Metab. **23**, 639–650 (2009)
27. P. Fofanova, N. Takamura, E. Kinoshita, A. Vorontson, V. Vladimirova, I. Dedov, V. Peterkova, S. Yamashita, MR imaging of the pituitary gland in children and young adults with congenital combined pituitary hormone deficiency associated with PROP1 mutations. Am. J. Roentgenol. **174**, 555–559 (2000)
28. A. Voutetakis, M. Argyropoulou, A. Sertedaki, S. Livadas, P. Xekouki, M. Maniati-Christidi, I. Bossis, N. Thalassinos, N. Patronas, C. Dacou-Voutetakis, Pituitary magnetic resonance imaging in 15 patients with Prop1 gene mutations: pituitary enlargement may originate from the intermediate lobe. J. Clin. Endocrinol. Metab. **89**, 2200–2206 (2004)
29. M.G. Abrao, M.V. Leite, L.R. Carvalho, A.E.C. Billerbeck, M.Y. Nishi, A.S. Barbosa, R.M. Martin, I.J.P. Arnhold, B.B. Mendonca, Combined pituitary hormone deficiency (CPHD) due to a complete *PROP1* deletion. Clin. Endocrinol. **65**, 294–300 (2006)
30. J.S. Parks, A. Tenore, A.M. Bongiovanni, R.T. Kirkland, Familial hypopituitarism with large sella turcica. N. Engl. J. Med. **298**, 698–702 (1978)

31. F.G. Riepe, C.J. Partsch, O. Blankenstein, H. Monig, R.W. Pfaffle, W.G. Sippell, Longitudinal imaging reveals pituitary enlargement preceding hypoplasia in two brothers with combined pituitary hormone deficiency attributable to PROP1 mutation. J. Clin. Endocrinol. Metab. **86**, 4353–4357 (2001)
32. C. Teinturier, S. Vallete, C. Adamsbaum, M. Bendaoud, T. Brue, P.F. Bougneres, Pseudotumor of the pituitary due to PROP-1 deletion. J. Clin. Endocrinol. Metab. **15**, 95–101 (2002)
33. A. Zygmunt-Gorska, J. Starzyk, D. Adamek, E. Radwanska, P. Sucharski, I. Herman-Sucharska, J.J. Pietrzyk, Pituitary enlargement in patient with PROP1 gene inactivating mutation represents cystic hyperplasia of the intermediate pituitary lobe. Histopathology and over 10 years follow-up of two patients. J. Pediatr. Endocrinol. Metab. **22**, 653–660 (2009)
34. R.D. Ward, L.T. Raetzman, H. Suh, B.M. Stone, I.O. Nasonkin, S.A. Camper, Role of PROP1 in pituitary gland growth. Endocrinol. **19**, 698–710 (2005)
35. J.A. Loh, J.G. Verbalis, Disorders of water and salt metabolism associated with pituitary disease. Endocrinol. Metab. Clin. North Am. **37**, 213–234 (2008)
36. J.G. Verbalis, S.R. Goldsmith, A. Greenberg, R.W. Schrier, R.H. Sterns, Hyponatremia treatment guidelines 2007: expert panel recommendations. Am. J. Med. **120**(suppl 1), S1–S21 (2007)
37. W.B. Schwartz, W. Bennett, S. Curelop, F.C. Bartter, A syndrome of renal sodium loss and hyponatremia probably resulting from inappropriate secretion of antidiuretic hormone. Am. J. Med. **23**, 529–542 (1957)
38. I.N. Mandell, R.A. DeFronzo, G.L. Robertson, F.N.J. Forrest, Role of plasma arginine vasopressin in the impaired water diuresis of isolated glucocorticoid deficiency in the rat. Kidney Int. **17**, 186–195 (1950)
39. W. Oelkers, Hyponatremia and inappropriate secretion of vasopressin (antidiuretic hormone) in patients with hypopituitarism. N. Engl. J. Med. **321**, 492–496 (1989)
40. R.H. Sterns, J.E. Riggs, S.S. Schochet Jr., Osmotic demyelination syndrome following correction of hyponatremia. N. Engl. J. Med. **314**, 1535–1542 (1986)
41. J.G. Verbalis, Hyponatremia. Endocrinologic causes and consequences of therapy. Trends Endocrinol. Metab. **3**, 1–7 (1992)
42. A. Perianayagam, R.H. Sterns, S.M. Silver, M. Grieff, R. Mayo, J. Hix, R. Kouides, DDAVP is effective in preventing and reversing inadvertent overcorrection of hyponatremia. Clin. J. Am. Soc. Nephrol. **3**, 331–336 (2008)