EClinicalMedicine 19 (2020) 100260

Contents lists available at ScienceDirect

EClinicalMedicine

journal homepage: https://www.journals.elsevier.com/eclinicalmedicine

Commentary

Pituitary abnormalities in midline brain defects

Stefano Zucchini

Pediatric Endocrine Unit, Department of Women's, Children's Health and Urologic Diseases, S. Orsola-Malpighi Hospital of Bologna, Italy

ARTICLE INFO

Article History:
Received 6 January 2020
Accepted 9 January 2020
Available online xxx

Pituitary is centrally located in the middle of the brain and embriologically originates from two different groups of cells, the first deriving from an upward protrusion of ectodermal cells from the pharynx (anterior pituitary), the second from a downward evagination of diencephalic neuroectodermal cells (posterior pituitary). Several genes are implicated in such a complex development (HESX1, OTX2, PROP1, POU1F1, LHX3, LHX4, SOX2/SOX3, and others) [1,2] and their mutations often cause congenital hypopituitarism, with possible deficiency of one or more hormones produced by the gland. Since the eye and the forebrain share a common embryological origin with the pituitary gland (mutations in the genes HESX1, SOX2/SOX3 and OTX2 has been found to affect both the embryonic development of the eyes, optic nerves and pituitary gland) [3], the association between pituitary and ocular defects are not rare. Among these, septo-optic dysplasia (SOD), firstly described in 1956 by the French-Swiss neurologist de Morsier [4], is the most known. Typically, SOD is characterized by optic nerve hypoplasia, agenesis of septum pellucidum and/or corpus callosum and finally by various degrees of pituitary hypoplasia. Its prevalence in Europe has recently been calculated between 1.9 and 2.5 per 100,000 births [5], therefore can be classified as rare disease (OMIM 182230). Phenotype is highly variable with only 30% presenting the classic triad: for the diagnosis of SOD, in fact, two out of the three above-mentioned signs are sufficient. If the pituitary is involved, growth hormone deficiency is the most frequent defect, followed by thyroid-stimulating hormone defect, adrenocorticotropin hormone, gonadotropins and less frequently arginine vasopressin with diabetes insipidus. As a whole, the clinical picture is complex: some have suggested to use the term SOD spectrum to include forms with a wider range of midline defects.

The recent retrospective-longitudinal study by Cerbone et al. [6], publishing a cohort of 171 cases examined longitudinally for 6–8 years in a single center, focused on endocrine function of patients with midline brain defects, including SOD, multiple pituitary hypoplasia and isolated optic nerve hypoplasia. The main aim of the study was to describe the endocrine morbidity and mortality of these three conditions. The results obtained were able to shed light on the complex clinical spectrum of SOD and on the subtypes of pituitary deficiencies in the three groups studied. The meticulous description of hormonal defects, encompassing from absent minipuberty to precocious puberty, from GH deficiency to the identification of 70 patterns of evolution of 16 types of associations of pituitary deficits, represents a compendium of endocrinology of the pituitary gland. GH deficiency was diagnosed with nocturnal mean concentration, and different degrees of hypopituitarism were evaluated through the Endocrine Morbidity Score. The careful reading of the manuscript may therefore significantly improve the knowledge and management of all patients with SOD. As for the simultaneous presence of diabetes insipidus, a more detailed description on the association may be found only in the study by Secco et al. [7], who specifically found in patients with SOD, complex brain abnormalities and ectopic posterior lobe, that the most common posterior dysfunction was hyperosmolality and relative AVP deficiency.

It was expected that patients with multiple pituitary hormone deficiencies presented with an earlier and more severe hormonal deficit compared to patients with SOD or isolated optic hypoplasia, and also that patients with SOD and simultaneous abnormalities of the pituitary stalk were similar to those with multiple pituitary deficiencies. Despite that, the manuscript provides detailed information and abundant graphical representations on the hormonal pictures of all the subtypes of SOD. Unfortunately, it is confirmed that genetic analysis, despite the various mutations published in the literature, is currently of little help in identifying the causative genetic error: also in the present study, in fact, the detection rate was less than 10%, with only 9 patients identified out of the 144 examined.

The study confirms the complexity of SOD, whose pituitary abnormalities span from no deficit, various degree of pituitary deficiencies to pituitary hyperfunction with precocious puberty. SOD still remains a complex syndrome and the authors could not demonstrate the initial pattern able to predict the outcome of pituitary function: this was true even if the morphologic aspects of the hypothalamus-pituitary structures were considered. It would be almost impossible, due to the complexity of all the combinations of pituitary deficiencies, to create an algorithm able to guide the endocrinologist towards an easier diagnosis and subsequent treatment.

Finally, the mortality rate, around 3–4%, was luckily low, limited to the patients with complex phenotypes and not necessarily due to insufficient endocrine replacement therapy: the country where the

DOI of original article: http://dx.doi.org/10.1016/j.eclinm.2019.11.017.
E-mail addresses: stefano.zucchini@aosp.bo.it, elozukk@libero.it

https://doi.org/10.1016/j.eclinm.2020.100260

study was led, has presumably an efficient National Health System, with specialists able to treat properly all patients with pituitary hormonal deficiencies.

As a whole, pituitary involvement in midline brain defect is common and multiple pituitary deficiencies are almost inevitable in case of pituitary stalk interruption and ectopic posterior pituitary, regardless the presence of optic nerve abnormalities. SOD is a complex syndrome with sometimes unpredictable endocrine outcome: only centres having an expert team made of pediatric endocrinologist, ophthalmologist, neurologist, cardiologist and others will be able to follow these complex patients and avoid sometimes life-threatening complications.

The findings obtained by Cerbone et al. thanks to the unique case series described, gives an extensive overview on the possible endocrine involvement in patients with SOD, optic nerve hypoplasia and multiple pituitary hormone deficiency, making every reader more expert in this difficult topic.

Declaration of Competing Interest

None.

References

[1] Alatzoglou KS, Dattani MT. Genetic forms of hypopituitarism and their manifestation in the neonatal period. Early Hum Dev 2009;85:705–12.
[2] França MM, Jorge AA, Carvalho LR, Costalonga EF, Vasques GA, Leite CC, Mendonca BB, Arnhold IJ. Novel heterozygous nonsense GLI2 mutations in patients with hypopituitarism and ectopic posterior pituitary lobe without holoprosencephaly. J Clin Endocrinol Metab 2010;95:E384–F391.
[3] McCabe M, Alatzoglou K, Dattani M. Septo-optic dysplasia andother midline defects: the role of transcription factors: HESX1 and beyond. Best Pract Res Clin Endocrinol Metab 2011;25(1):115–24.
[4] De Morsier G. Studies on malformation of cranioencephalic sutures. III. agenesis of the septum lucidum with malformation of the optic tract. Schweiz Arch Neurol Psychiatr 1956;77(1−2):267–92.
[5] Garne E, Rissmann A, Addor MC, Barisic I, Bergman J, Braz P, et al. Epidemiology of septo-optic dysplasia with focus on prevalence and maternal age – a Eurocat study. Eur J Med Genet. 2018;61(9):483–8.
[6] Cerbone E, Güemes M, Wade A, Improda N, Dattani MT. Endocrine morbidity in midline brain defects: differences between septo-optic dysplasia and related disorders. EClinicalMedicine 2020. doi: 10.1016/j.eclinm.2019.11.017.
[7] Secco A, Allegri AE, di Iorgi N, Napoli F, Calcagno A, Bertelli E, Olivieri I, Pala G, Parodi S, Gastaldi R, Rossi A, Maghnie M. Posterior pituitary (PP) evaluation in patients with anterior pituitary defect associated with ectopic PP and septo-optic dysplasia. Eur J Endocrinol 2011;165(3):411–20.