Case Report

Novel Variant in Exon 3 of the BMP4 Gene Resulted in Ectopic Posterior Pituitary, Craniocervical Junction Dysmorphism and Limb Anomaly

Valeria Calcaterra,1,2 Rossella Lamberti,2 Claudia Viggiano,2 Paola Baldassarre,2 Luigina Spaccini,3 Rosa Maria Alfano,4 Giana Izzo,5 Laura Grazia Valentini,6 and Gianvincenzo Zuccotti2,7

1Pediatric and Adolescent Unit, Department of Internal Medicine, University of Pavia, Pavia, Italy
2Department of Pediatrics, Pediatric Unit, “Vittore Buzzi” Children’s Hospital, Milan, Italy
3Clinical Genetics Unit, Department of Obstetrics and Gynecology, “V. Buzzi” Children’s Hospital, University of Milan, Italy
4Human Pathology, ASST Santi Paolo e Carlo, San Paolo Hospital, Milan, Italy
5Pediatric Radiology and Neuroradiology Unit, “Vittore Buzzi” Children’s Hospital, Milan, Italy
6Department of Neurosurgery, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy
7Department of Biomedical and Clinical Science “L. Sacco”, University of Milan, Milan, Italy

Correspondence should be addressed to Valeria Calcaterra; valeria.calcaterra@unipv.it

Received 11 February 2022; Revised 7 April 2022; Accepted 9 May 2022; Published 19 May 2022

Academic Editor: Isolina Riaño Galán

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Introduction. Pituitary differentiation involves a large number of transcription factors. In particular, BMP4 expression is fundamental for pituitary gland commitment from the ventral diencephalon, suppressing Shh expression in Rathke’s pouch. Pathogenic variants in BMP4 are reported in the literature with a broad phenotypic spectrum, including pituitary and brain malformations. Case Presentation. A five-year-old girl came to medical attention following a mild cervical trauma with onset of cervical pain. On clinical examination at birth, postaxial polydactyly type B of the left hand was observed and removed at 10 months of age. A cervical radiography was performed, and a suspicion of craniocervical junction malformation was made. A magnetic resonance imaging of the cervical spine was made, showing an ectopic posterior pituitary, associated with dysmorphism of the craniocervical junction. The anthropometric parameters were pubertal Tanner stage 1, weight 16 kg (z-score: −1.09), height 107 cm (z-score: −0.76), and BMI 14 kg/m² (z-score: −0.92). Normal hormonal assessment was detected. Genetic analysis via next generation sequencing showed a novel de novo heterozygous variant (c.277G>T, p.Glu93*) in exon 3 of BMP4. Discussion. We described a novel mutation in BMP4, resulting in ectopic posterior pituitary with normal hormonal assessment, associated to craniocervical junction dysmorphism and limb anomaly. It is important to monitor patient’s growth and puberty and to screen the onset of symptoms related to the deficiency of one or more anterior as well as posterior pituitary hormones.

1. Introduction

The pituitary gland is responsible for the regulation of growth, reproduction, and metabolism. It is formed by three lobes with different embryological origins: the anterior and the intermediate lobes derive from the oral ectoderm (Rathke’s pouch), while the posterior lobe derives from the neural ectoderm [1, 2]. The development of the anterior gland leads to the differentiation of cell types which secret different hormones including growth hormone (GH), thyroid-stimulating hormone (TSH), prolactin (PRL), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and adrenocorticotropic hormone (ACTH). The intermediate lobe comprehends cells which secrete proopiomelanocortin
The posterior gland or neurohypophysis is constituted by the axonal terminals of neurons from the paraventricular and supraoptic nuclei of the hypothalamus, which secrete oxytocin and vasopressin, respectively [1, 3]. The release of the pituitary hormones depends on the control of the hypothalamic factors, such as thyrotrophin-releasing hormone (TRH), corticotrophin-releasing hormone (CRH), gonadotrophin-releasing hormone (GnRH), growth hormone releasing hormone (GHRH), dopamine, and somatostatin (SS) [1–4].

The signalling mechanism in pituitary morphogenesis involves a lot of transcription factors (Shh, P-OTX/Pit1/2, BMP4, FGF8, HESX1, PROP1, POU1F1, LHX3, LHX4, PITX1, PITX2, SOX2, and SOX3) [5–7]. In particular, BMP4 expression is fundamental in the limbs, heart, facial processes, and mesenchymal cells development. BMP4 is responsible for pituitary gland commitment from the ventral diencephalon, suppressing Shh expression in Rathke’s pouch [8, 9]. Pathogenic variants in BMP4 are reported in the literature with a broad phenotypic spectrum which includes eye anomalies (exophthalmia, anophthalmia, microphthalmia, and sclerocornea), hands and/or feet postaxial polydactyly, ventriculomegaly, reduction of white matter, eye anomalies (exophthalmia, anophthalmia, microphthalmia, and sclerocornea), hands and/or feet postaxial polydactyly, ventriculomegaly, reduction of white matter, and several biological functions [13]. Initially described as involved in the bone formation, BMPs play crucial roles in many organ systems [14].

BMP family members induce differentiation of bone lineage cells and regulate cellular division, apoptosis, cellular differentiation, and morphogenesis. In particular, BMP4 is involved in the process of embryogenesis (mesodermal development, cellular commitment during and after the gastrulation process, and tissue development in the lungs, liver, kidney, urinary system, and teeth) [13, 15, 16]. Moreover, BMP4 is essential in the initial steps of the development of adenohypophysis. In fact, the onset of pituitary organogenesis is characterized by the restriction of Shh, BMP4, FGF8, and Wnt5a, which are expressed in the oral ectoderm from the invaginating Rathke pouch [13, 17].

As described in literature, a homozygous mutation of BMP4 in mice was lethal, while a heterozygous mutation of this gene caused skeletal abnormalities including polydactyly [9, 18, 19]. It was also described that BMP4 heterozygous null mice is associated with ocular anterior segment abnormalities [20, 21].

In this case report, we described a novel variant in BMP4 resulted in ectopic posterior pituitary, craniofacial dystrophy, and limb anomaly.

The bone morphogenetic proteins (BMPs) are members of the transforming growth factor-β (TGF-β) superfamily. TGF-β is a group of cytokines with ubiquitous distribution and several biological functions [13]. Initially described as involved in the bone formation, BMPs play crucial roles in many organ systems [14]. BMP family members induce differentiation of bone lineage cells and regulate cellular division, apoptosis, cellular differentiation, and morphogenesis. In particular, BMP4 is involved in the process of embryogenesis (mesodermal development, cellular commitment during and after the gastrulation process, and tissue development in the lungs, liver, kidney, urinary system, and teeth) [13, 15, 16]. Moreover, BMP4 is essential in the initial steps of the development of adenohypophysis. In fact, the onset of pituitary organogenesis is characterized by the restriction of Shh, BMP4, FGF8, and Wnt5a, which are expressed in the oral ectoderm from the invaginating Rathke pouch [13, 17].

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An endocrinological check-up was performed. The anthropometric evaluation showed weight 16 kg (WHO z-score: −1.09), height 107 cm (WHO z-score: −0.76), and BMI 14 kg/m² (WHO z-score: −0.92), with a pubertal Tanner stage 1.

As given in Table 1, the hormonal dosages (TSH, FT3, FT4, LH, FSH, PRL, ACTH, cortisol, and IGFI) were in range according to the age. Concordance between skeletal age and chronological age was detected.

Furthermore, genetic analysis was performed. DNA was extracted from peripheral blood of both the proband and the parents (QIAamp, DNA mini kit, Qiagen, Germany). Genomic DNA was enriched for the targeted exome with the TSO (TruSight One,临床 exome) (Illumina, San Diego, CA, USA) kit according to the manufacturer’s protocol and sequenced on the Illumina MiSeq platform.

Exome sequencing identified a heterozygous missense variant in BMP4: c.277G > T; p.(Glu93?) in exon 3 (RefSeq NM_001202.3). The variant has been confirmed with Sanger technology, is de novo, absent in the parents, is not reported in the literature, and is not described in the database of polymorphisms (ExAC, gnomAD). This variant is predicted as damaging by several prediction tools and (SIFT, PolyPhen, MutationTaster, FATHMM, VarSome) classified as pathogenic (PVS1,PM2,PP3) according ACMG guidelines [12].

A long-term endocrinological monitoring was proposed and accepted.

3. Discussion

In this case report, we described a novel variant in BMP4 resulted in ectopic posterior pituitary, craniofacial dysmorphism, and limb anomaly.

The bone morphogenetic proteins (BMPs) are members of the transforming growth factor-β (TGF-β) superfamily. TGF-β is a group of cytokines with ubiquitous distribution and several biological functions [13]. Initially described as involved in the bone formation, BMPs play crucial roles in many organ systems [14]. BMP family members induce differentiation of bone lineage cells and regulate cellular division, apoptosis, cellular differentiation, and morphogenesis. In particular, BMP4 is involved in the process of embryogenesis (mesodermal development, cellular commitment during and after the gastrulation process, and tissue development in the lungs, liver, kidney, urinary system, and teeth) [13, 15, 16].

Moreover, BMP4 is essential in the initial steps of the development of adenohypophysis. In fact, the onset of pituitary organogenesis is characterized by the restriction of Shh, BMP4, FGF8, and Wnt5a, which are expressed in the oral ectoderm from the invaginating Rathke pouch [13, 17].

As described in literature, a homozygous mutation of BMP4 in mice was lethal, while a heterozygous mutation of this gene caused skeletal abnormalities including polydactyly [9, 18, 19]. It was also described that BMP4 heterozygous null mice is associated with ocular anterior segment abnormalities [20, 21].
Patients with BMP4 deletions could manifest ocular anomalies, anterior segment dysgenesis with microcornea, and pituitary and brain malformations [22]. Recently, Jaing et al. [23] reported a novel ocular phenotype, characterized by the pathologic myopia rather than microphthalmia, in heterozygous BMP4 truncations.

Indeed, pathogenic variants in BMP4 are reported in the literature with a broad phenotypic spectrum which includes eye anomalies (exophthalmia, anophthalmia, microphthalmia, and sclerocornea), hands and/or feet postaxial polydactyly, ventriculomegaly, reduction of white matter, hypoplasia of the corpus callosum at brain MRI, some minor abnormalities of the face, delayed psychomotor development, and variable intellectual disability [10, 11].

However, different phenotypes among patients with the same BMP4 mutation suggest complex clinical features caused by BMP4 dysfunction [24].

In our case report, a novel de novo heterozygous variant was detected (c.277 G > T, p.Glu93*) in exon 3 of BMP4, which confers a clinical disorder characterized by polydactyly type B, ectopy of neurohypophysis and dysmorphism of the craniocervical junction. We classified the variant as pathogenic according to ACMG guidelines that deal with evolutionary conservation of DNA sequences and amino acid; functional studies could be useful to define the protein resulting from posttranslational processing and dimerization of the BMP4 peptide.

Genetic heterogeneity and variable penetrance of this mutation makes genetic diagnosis difficult considering that posterior pituitary ectopia may not present hormonal disturbance [25]. Additionally, as proposed by Rodriguez-Contreras [26], an oligogenic inheritance may contribute to modify phenotypic expressivity of BMP4 pathogenic variants.

Once ectopic posterior pituitary has been discovered, from an endocrinological point of view, it is important to monitor patient’s growth and puberty and to screen the onset of symptoms related to the deficiency of one or more anterior as well as posterior pituitary hormones.

**Data Availability**

The data used to support this study are available from the corresponding author upon request.

**Consent**

Written informed consent was obtained from participants and their parents for publication of the details of their medical case and any accompanying images.

**Conflicts of Interest**

The authors declare that they have no conflicts of interest.

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