Duplication of the pituitary gland - plus syndrome

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Abstract

Duplication of the pituitary gland (DPG) is a very rare developmental anomaly that is often associated with other anomalies – the DPG-plus syndrome and occurs due to splitting of the rostral notochord and prechordal plate during blastogenesis. DPG with the constellation of associated anomalies as in our patient has not been reported previously. This article illustrates the importance of imaging the brain in all patients with obvious midline facial anomalies and the complementary role of MRI and CT in such cases.

Key words: Basilar artery duplication; blastogenesis; craniopharyngeal canal; duplication of pituitary gland; epignathus teratoma

Introduction

Duplications of internal organs are rare. They occur either due to non-union of anlages or division of the primordial organ. Duplication of the pituitary gland (DPG) is a very rare developmental anomaly, with only 40 cases reported till 2012.[1-3] With DPG as the common denominator, a large number of associated anomalies have been reported - the DPG-plus syndrome.[1] In this article, we report a case of pituitary duplication that was associated with duplication of the sella, hypertelorism, cleft palate, a large craniopharyngeal canal and oropharyngeal teratoma, hypoplastic olfactory bulbs and tracts, duplication of the basilar artery, and cervical anterior cleft vertebrae. DPG with this constellation of associated anomalies in the same patient has, to the best of our knowledge, not been reported previously.

Case Report

A 10-month-old female infant, born of a non-consanguinous marriage by normal delivery at full term, was brought by her mother to the hospital with the history of a congenital cleft palate. A mass was also present within the cleft. Pending definitive corrective surgery, the cleft had been initially managed with an obturator. After about 7 months of age, the mass started gradually increasing in size with resultant breathing difficulty. The baby's life was otherwise uneventful with normal weight gain and achievement of milestones. There was no history of similar illness in the family. The cleft had been detected on antenatal ultrasonography (USG); however, the oropharyngeal mass had not been detected. The course of the pregnancy had been otherwise uneventful and there was no history of polyhydramnios.

On examination, the baby had hypertelorism [Figure 1A]. Growth parameters and developmental milestones were normal. The neurological and fundus examination did not reveal any abnormality. Oral examination revealed a midline cleft involving the hard and soft palates without involvement of the alveolus. A fleshy mass was seen through the cleft and some hemorrhage was also noted on its surface [Figure 1B]. Serum alpha-fetoprotein (AFP) and beta-human chorionic gonadotropin (β-hCG) levels were not elevated. All hematological and other biochemical tests were normal. The chest radiograph and abdominal USG were normal.

Non-contrast enhanced magnetic resonance imaging (MRI) (Symphony Tim 1.5T MRI scanner, Siemens, Erlangen, Germany) of the patient was performed to evaluate the mass, which revealed a large craniopharyngeal canal extending anteroinferiorly from a location just anterior

Figure 1 (A-E): Photographs of the infant showing (A) hypertelorism and (B) median cleft palate. A fleshy mass is seen through the defect. The panel of sagittal (C) T1W, (D) T2W and (E) T1W fat-suppressed MRI imags reveals tubo-mamillary fusion (thin white arrows). A large craniopharyngeal canal is seen with a nasopharyngeal mass at its caudal end (solid arrows). The mass is heterogeneously hyperintense on both T1W and T2W images, with signal loss on fat-suppressed images

to the sella. At the caudal end of the canal, a lobulated oropharyngeal mass (25.9 mm × 13.0 mm × 16.3 mm; anteroposterior × transverse × craniocaudal) was noted extending up to the palatal cleft. There was no intracranial extension. The mass was heterogeneous in signal intensity; an area that appeared heterogeneously hyperintense on both T1W and T2W images, with signal loss on fat-suppressed images was noted within it. Peg-like structures that were markedly hypointense on both T1W and T2W images were seen within the superior aspect of the mass [Figure 1C-E]. These findings were suggestive of an oropharyngeal teratoma (epignathus teratoma).Note was made of an osseous spine dividing the sella, DPG with two separate pituitary stalks, and widening of the optic chiasma (17.6 mm) [Figure 2]. Tubomamillary fusion (hypothalamic pseudohamartoma) was also noted with thickening of the floor of the third ventricle and two separate infundibular recesses [Figures 1 and 2]. Corroborative computerized tomography (CT) (Somatom Sensation 16, Siemens, Erlangen, Germany) images confirmed the osseous

spine dividing the sella and the large (9.3 mm × 6.8 mm; anteroposterior × transverse) craniopharyngeal canal with tooth-like calcified structures within its caudal end. The vomer bone was detected to be widened posteriorly with a transverse diameter of 9.3 mm (normally less than 1.5 mm in diameter) with narrowing of the choanae [Figure 3]. MRI also revealed duplication of the rostral part of the basilar artery with each superior cerebellar and posterior cerebral artery originating from the respective ipsilateral basilar artery [Figure 4A and 4B]. Hypoplasia of bilateral olfactory bulbs [Figure 4C] and anterior clefting of the cervical vertebrae were also noted [Figure 4D]. The rest of the infant's brain was normal.

The infant's karyotype was normal (46, XX). The oropharyngeal mass was resected and confirmed to be a benign teratoma on histopathology. Subsequently, a single-stage closure of the median cleft was performed. The patient is on regular follow-up and there has been no recurrence of the growth or development of precocious puberty.

Discussion

DPG is a very rare developmental anomaly with only 40 cases reported till 2012.[1-3] It has been reported in both the pediatric and adult populations. Most patients are females.[1-3] DPG is usually detected in unsuspected patients on imaging due to the associated midline craniofacial anomalies.[4] The rarity of this entity may hence be partially attributable to incidental detection on imaging and early mortality in some patients. While most patients have been diagnosed in the neonatal period, later detection has been due to evaluation for anosmia, delayed onset of puberty and menarche, and precocious puberty.[5,6]

DPG is frequently associated with multiple other craniofacial defects like broadening or duplication of the sella, broadening of the optic chiasma, duplication of the infundibulum, tubo-mamillary fusion (hypothalamic

Figure 2 (A and B): (A) Coronal T1W and (B) T2W MRI images show duplication of the pituitary gland with two pituitary stalks (thin white arrows) and neurohypophyseal "bright" spots (thick white arrows). The optic chiasma is also widened. The floor of the third ventricle is thickened and there are two infundibular recesses (arrows)

pseudohamartoma), duplication of the basilar artery, agenesis/hypoplasia of the corpus callosum, hypertelorism, cleft palate, craniopharyngeal canal, oropharyngeal teratomas, and vertebral segmentation anomalies.[1,5] Other rare associations that have been reported include duplication of the lips, tongue, mandible; a wide cribriform plate; absent olfactory bulbs and/or tracts; cerebellar hypoplasia; ventricular enlargement; pontine hypoplasia; neuronal migration abnormalities; and supernumerary teeth.[1,5] Apart from anomalies of the head and neck region, congenital diaphragmatic hernia has been associated with DPG.[1] The high association of these craniofacial anomalies with DPG is suggestive of a polytopic blastogenesis defect, and hence, Manjila, et al.[1] have proposed the term *DPG-plus syndrome.*

The various theories that have been propounded in the past to explain the occurrence of DPG include incomplete twinning, teratogens, and extreme clefting.[1,5] However, these theories are not tenable as twinning would involve all facial structures, a specific teratogen that is consistently associated has not yet been identified, and median cleft would not involve the brain and its circulation. The most plausible explanation for DPG-plus syndrome, as proposed by Morton, is splitting of the rostral notochord and prechordal plate during blastogenesis.[7] Any defects occurring in this stage are often severe with involvement of multiple midline organs.[8]

The development of the pituitary gland is a very complex process that occurs in proximity to the notochord and prechordal plate, and is closely linked to the development
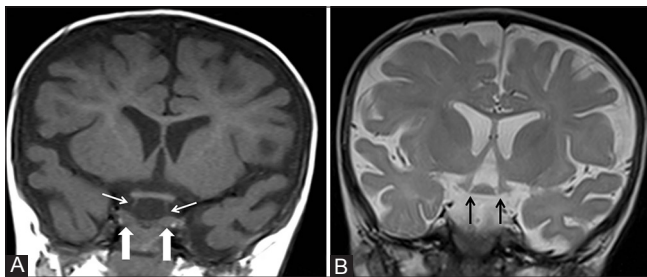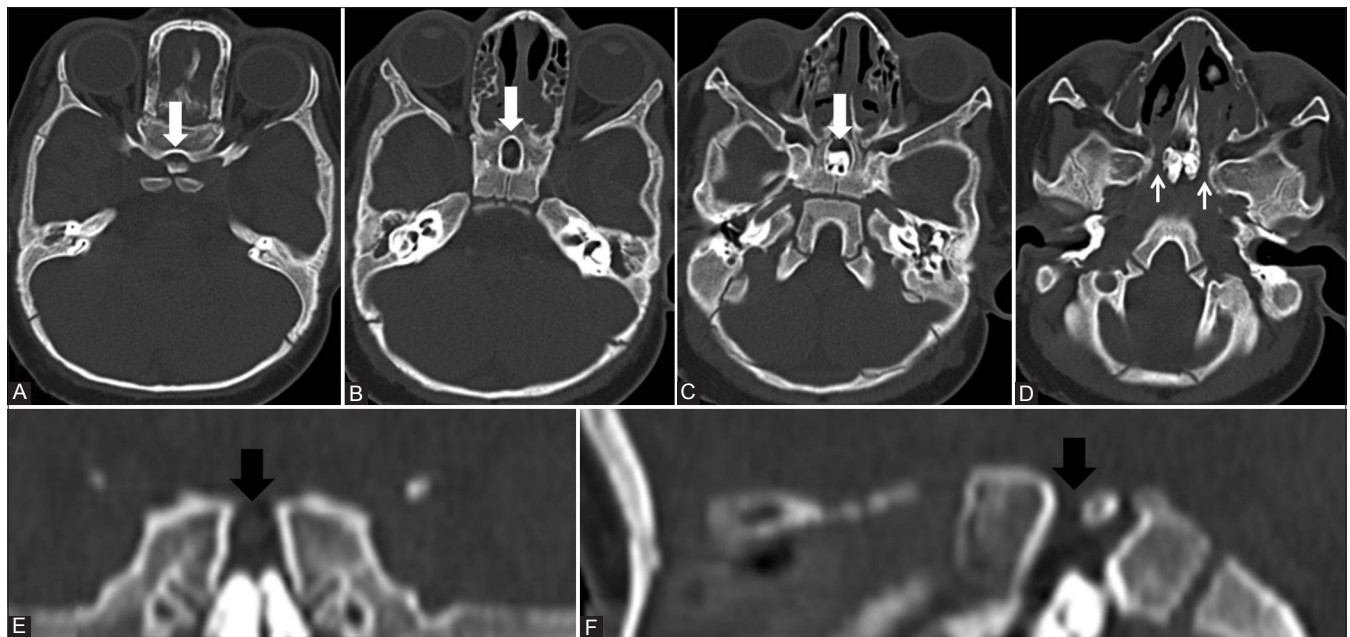

Figure 3 (A-F): The panel of axial (craniocaudal) CT images in bone window (A-D) reveals a large craniopharyngeal canal (thick white arrows). The duplicated sella with an intervening sellar spine is seen in (A). The narrowed posterior choanae are also seen (thin arrows). Coronal (E) and sagittal (F) reformatted CT images showthe large craniopharyngeal canal (thick black arrows) with dense tooth-like structures
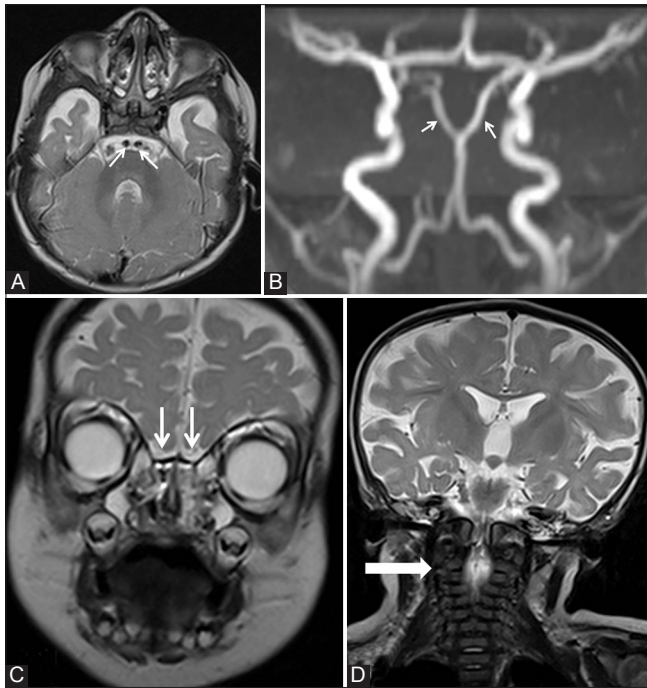
Figure 4 (A-D): (A) T2W axial and (B) maximum intensity projection (MIP) MRI images show duplication of the basilar artery. The superior cerebellar and posterior cerebral arteries are seen originating from the respective ipsilateral basilar artery. (C and D) T2W coronal MRI images show hypoplasia of bilateral olfactory bulbs/tracts (thin white arrows) and anterior clefting of the cervical vertebrae

of the prosencephalon (forebrain). At around 22 days, the oral ectoderm and neural ectoderm at the floor of the diencephalon are juxtaposed. Differential growth of the forebrain and the gut tube creates the infundibular recess and Rathke's cleft, respectively, at around 28 days. By around day 37, the Rathke's pouch gradually loses its connection with the oral cavity due to growth of the sphenoid cartilage with an occasional small residual pharyngeal hypophysis. The anterior and intermediate lobes of the pituitary are thus derived from the oral ectoderm (Rathke's pouch), while the posterior pituitary originates from neural ectoderm (infundibulum). These tissue interactions occur due to multiple signaling molecules derived from genes like the *HOX* (homeobox) expressed in the notochord, prechordal plate, and neural plate; *BMP4* (bone morphogenetic protein 4) and *FGF8* (fibroblast growth factor 8) from the ventral forebrain; and *SHH* (sonic hedgehog) from the notochord.[9,10] As the notochord induces formation of the pituitary plaque, any early insult causing splitting of the notochord or prechordal plate would also lead to DPG. Tubo-mamillary fusion, as seen in our case, is the most frequently associated anomaly in DPG and is probably due to arrest of lateral migration of cells that form the hypothalamic nuclei consequent to the aforementioned notochordal insult.[6] This cellular derangement may be responsible for precocious puberty or delayed onset of puberty/menarche.

The skull base develops by enchondral ossification. The body of the sphenoid bone is mainly formed by the presphenoid and postsphenoid centers. The portion anterior to the tuberculum sellae and chiasmatic sulcus is formed by the presphenoid. The postsphenoid portion forms the portion posterior to the tuberculum sellae, and consists of medial and lateral ossification centers on either side. The synchondrosis between the medial postsphenoid centers at the border of the tuberculum sellae represents the craniopharyngeal canal and is thought to be a remnant of the Rathke's pouch.[11] The term "craniopharyngeal canal"or "persistent hypophyseal canal" usually refers to a small and vertical midline defect that measures less than 1.5 mm in diameter. Its incidence in adults is 0.42%; however, it is rarely seen on imaging due to its small size.[12] Currarino, *et al.* have used the terms"large craniopharyngeal canal" and "trans-sphenoidal canal" for canals that are larger in diameter and often associated with craniofacial anomalies like hypertelorism, facial cleft, cleft lip and palate, ocular and optic tract anomalies, agenesis of corpus callosum, and nasopharyngeal mass.[13] The sellar spine is thought to be a remnant of the cephalic tip of the notochord.[14]

"Epignathus" teratoma is a non-site-specific generic term that is applied to oropharyngeal teratomas in neonates.[15] They are generally mature, benign teratomas, seen in female neonates born to young mothers and are often associated with polyhydramnios due to mechanical impediment to swallowing.[3,15] These tumors most commonly originate from the pharyngeal end of the craniopharyngeal canal with infrequent intracranial extension.[15] The karyotype of the tumor cells is identical to that of the other normal somatic cells, indicating a mitotic origin from a totipotential diploid cell.[15] These tumors are known to exert mass effect causing mandibular duplication/expansion, remodeling of the oropharyngeal cavity, prevention of palatal closure, and bifid tongue or nose.[3,15]

Segmental duplication or fenestration of the basilar artery has a prevalence of 0.04-0.6% and 5.26% on angiography and autopsy, respectively. It occurs due to failure of craniocaudal fusion of the embryonic longitudinal neural arteries into the basilar artery and failure of regression of the bridging arteries that connect the longitudinal arteries, and generally involves the caudal portion of the basilar artery.[4] Involvement of the rostral segment of the basilar artery, though otherwise very rare, is relatively more frequent in DPG.[4,16] An increased risk of aneurysm formation has been noted in patients with fenestration of the basilar artery due to altered hemodynamics.[4]

Thus, these anomalies in our patient as well as the spectrum of other associated anomalies in DPG-plus syndrome can all be explained based on the theory of rostral notochordal splitting during blastogenesis. MRI of the brain is essential in all patients with obvious midline facial anomalies.

T1W, T2W and fluid attenuated inversion recovery (FLAIR) axial, and T2W sagittal and coronal images should be acquired in all such patients. The field-of-view (FOV) during acquisition of the sagittal and coronal images should be such as to include the cervical spine. Detection of tubo-mamillary fusion should prompt a dedicated sellar imaging protocol. These sequences may be supplemented by non-contrast and contrast-enhanced fat-suppressed images when a craniopharyngeal mass is detected. Vascular anomalies detected on T2W axial and coronal images may be better delineated by 3D-Time of Flight (3D-TOF) MR angiography (MRA). CT scan has a complementary role as it better delineates osseous craniofacial anomalies and affords 3D reconstructions and surface rendering for pre-surgical planning. Due to the high association of flow-related aneurysms with duplications and fenestrations, periodic surveillance for aneurysms is also warranted. Notwithstanding the rarity of associated anomalies outside the central nervous system or the spine, a chest radiograph and an abdominal USG should be considered.

The management of such patients is multi-disciplinary and patient-specific depending on the associated anomalies and presence of precocious puberty. Precocious puberty is treated with gonadotropin-releasing hormone (GnRH) analogs. If there is an associated epignathus teratoma, its management is determined by its size, degree of airway compromise, intracranial extension and secondary mechanical remodeling of the oropharyngeal airway, and prevention of palatal closure. Depending on the gravity of the situation, intubation followed by partial or complete resection is performed immediately after birth or within 3 weeks. This is followed by staged reconstructive procedures between 1 month and 3 years of age.[3] If there is no airway compromise, the resection of the mass may be delayed and combined with other reconstructive surgeries as was done in our patient.

Conclusion

DPG is a very rare developmental anomaly that occurs due to splitting of the rostral notochord and prechordal plate during blastogenesis. It is often associated with a large number of associated craniofacial anomalies and, hence, the appellation the DPG-plus syndrome. This case illustrates that it may be worthwhile imaging the brain in all patients with obvious midline facial anomalies and a dedicated sellar protocol in the presence of tubo-mamillary fusion. While MRI is the primary modality of imaging in such patients, the complementary role of CT scan is also highlighted.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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