Case Report

Duplication of the pituitary gland associated with multiple blastogenesis defects: Duplication of the pituitary gland (DPG)-plus syndrome. Case report and review of literature

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Abstract

Background: Duplication of the pituitary gland (DPG) is a rare craniofacial developmental anomaly occurring during blastogenesis with postulated etiology such as incomplete twinning, teratogens, median cleft face syndrome or splitting of the notochord. The complex craniocaudal spectrum of blastogenesis defects associated with DPG is examined with an illustrative case.

Case Description: We report for the first time in the medical literature some unique associations with DPG, such as a clival encephalocele, third cerebral peduncle, duplicate odontoid process and a double tongue with independent volitional control. This patient also has the previously reported common associations such as duplicated sella, cleft palate, hypertelorism, callosal agenesis, hypothalamic enlargement, nasopharyngeal teratoma, fenestrated basilar artery and supernumerary teeth. This study also reviews 37 cases of DPG identified through MEDLINE literature search from 1880 to 2011. It provides a detailed analysis of the current case through physical examination and imaging.

Conclusion: The authors propose that the developmental deformities associated with duplication of pituitary gland (DPG) occur as part of a developmental continuum, not as chance associations. Considering the fact that DPG is uniquely and certainly present throughout the spectrum of these blastogenesis defects, we suggest the term DPG-plus syndrome.

Key Words: Blastogenesis, clival encephalocele, diprosopus, duplication of the pituitary gland, split notochord

INTRODUCTION

Duplication of the pituitary gland (DPG) is an extremely rare malformation that has been described in fewer than 40 cases since 1880. Several mechanisms have been proposed for DPG: partial twinning, prenatal teratogen exposure, extreme presentation of the median cleft face syndrome or splitting of the notochord during blastogenesis. DPG is associated with various clinical findings that represent a continuum of defects
in blastogenesis. These associated features include cleft palate, bifid tongue, hypertelorism, callosal agenesis, nasopharyngeal teratoma, and absence of the olfactory bulb. We present a case of an eleven-year-old girl with all of the above listed features in addition to a clival encephalocele, third cerebral peduncle, duplicated odontoid process and double tongue which, to the best of our knowledge, have not been previously reported. Other published cases of DPG have been associated with only a few of these additional features. Considering the fact that DPG is uniquely and certainly present in all these blastogenesis defects, we propose that these defects occur as part of a syndrome continuum, not as chance association. The authors have hence termed these malformations as DPG-plus syndrome.

**CASE REPORT**

We present an eleven-year-old African-American female patient with multiple craniofacial anomalies that we speculate to have occurred during blastogenesis. She demonstrates duplication of both bony and soft tissue midline facial and cranial structures. Facial abnormalities include turribrachycephaly, flattened midface, hypertelorism, cleft palate, bilateral cleft lower lip, supernumerary teeth, macrostomia, short neck with limited range of movement and two separate, fully formed, independently moving tongues – double tongue [Figure 1a]. The mouth could not be opened for examination due to severe retrognathia, ankylosis of the TMJ and fibrosis of the masseters.

The patient demonstrates severe intellectual disability; she is nonverbal and does not follow commands but does point to things she wants. Cranial nerves are difficult to assess on examination. Visual acuity could not be reliably tested. However, she is able to recognize people and objects. Cranial nerves III-VII are unremarkable, CNVIII demonstrates profound hearing loss, and cranial nerves X, XI, XII are normal except for volitional independent control of both tongues.

The patient has a thoracic scoliosis of 55 degrees. Her height is in the 3rd percentile, weight in the 10th percentile. She has thin arms up and spreading her legs for diaper changes. She demonstrates profound hearing loss, and cranial nerves III-VII are unremarkable, CNVIII demonstrates profound hearing loss, and cranial nerves X, XI, XII are normal except for volitional independent control of both tongues.

The patient was born to a previously healthy G4P3 mother with a pregnancy complicated by failure of maternal weight gain and polyhydramnios noted during the last 2 weeks of gestation. Her mother denies medication use, drug or alcohol abuse. Early ultrasound did not reveal any abnormalities due to a large fibroid causing poor visualization of fetal parts. An ultrasound in the third trimester showed no gross deformities, but an absent lower lip. Three healthy older siblings show no similar abnormalities. Her parents are not consanguineous and there is no family history of malformations. The child was born via cesarean section due to fetal bradycardia at full term. Apgar scores were 4/7 and she was noted to have a mass in the anterior lower jaw, filling the oral cavity and extending into the posterior fossa. The mass prevented intubation but she responded to suctioning and chest compressions. She remained hypercapnic with a pCO₂ of 81 necessitating a tracheostomy at 2 days of age. The intraoral mass was biopsied at this time and found to be a mature teratoma. A gastrostomy tube was placed soon after for feeding. Severe reflux necessitated a Nissen fundoplication after G tube placement.

An incomplete resection of the oropharyngeal tumor was performed at 15 months of age. The tumor originated on the posterior aspect of the mandible and extended posteriorly to the pharynx and superiorly into the nasal cavity to the level of the crista galli. It was completely intraoral; only retrognathia and cleft lip were visible exteriorly. Intra-operatively, the tumor was found to have prevented fusion of the palatal shelves, creating a cleft palate. It had also grown inferiorly, creating two completely separate tongues extending back to the foramen cecum; the double tongue, however, was not surgically corrected to monitor recurrence of the teratoma. Resection of the tumor necessitated removal of the alveolar ridge of the mandible and most of the nasal septum. Posteriorly, the dissection was stopped at the level of the cranial base to prevent surgical entry into

![Figure 1: Demonstration of facial abnormalities (a) full body view showing scoliosis, frontal view demonstrating hypertelorism and cleft lip and image of mouth showing supernumerary teeth (b) demonstration of independent movement of double tongues: right tongue withdrawn while left protrudes](image-url)
the cranial cavity with the risk of subsequent CSF leak or infection. The final pathology of the tumor was mature teratoma. Residual tumor was left behind in the posterior fossa in the region of the clival encephalocele.

The past medical history is remarkable for multiple surgical interventions. Volvulus at age 7 required partial ileal and colon resection leading to short gut syndrome. She has also had soft tissue release and anterior tibial transfer performed on the left foot for a tight heel cord. The patient has a history of self-mutilation, including hand biting, scratching and hair pulling when she is upset, requiring frequent restraints. She has been home schooled due to infection risk.

Head MRI reveals duplication of multiple midline structures: two sellas and two pituitary glands, a duplicate ventricular system, two basilar arteries and a midline third cerebral peduncle [Figures 2a-c and 3a, b]. Her imaging is also notable for agenesis of the corpus callosum and a clival encephalocele Figure 3 with an adjacent midline nasopharyngeal tumor consistent with residual teratoma [Figure 4]. The craniocervical junction appeared abnormal with a widened C1 arch, C2 body duplication and two odontoid processes [Figure 5].

Karyotype from teratoma demonstrated normal chromosomes with 60:40 X inactivation. Telomeres were normal. A microarray based comparative genomic hybridization analysis of 3,397 loci using oligonucleotide probes was normal (Nimble Gen 135K).

**DISCUSSION**

Duplication of the pituitary gland (DPG) has been reported in the medical literature in both the pediatric and the adult population. Discussion of pituitary...
Twinning will generally result in a duplication of the hypophysis; hence, an early developmental insult must be considered when examining the development of the hypophysis to vividly understand the process of duplication and associated anomalies.

**Development of the pituitary gland**

The development of the human hypophyseal, or pituitary gland, has been widely studied due to its complex origin from multiple tissues.\[^{[31]}\] Despite the fact that the hypophysis contains two independent segments, the adenohypophysis and the neurohypophysis, they develop as a single structure.\[^{[19]}\] Ectoderm representing the adenohypophysis is present by day 22 at a location just rostral to the oropharyngeal membrane. This region contacts the neural plate in the area that will become the floor of the diencephalon.\[^{[9,31]}\] As the telencephalon grows in both anterior and posterior directions, the adherence between these tissues creates the infundibular recess in the neural plate. At 28 days, this expansion of the embryo as well as the continued expansion of the gut tube creates Rathke’s pouch: as the pharynx grows, the ectoderm that will become the adenohypophysis remains adherent to the neural tissue of the future neurohypophysis. This adenohypophysis tissue is ‘left behind,’ creating the invagination known as Rathke’s pouch as the walls of the pharynx grow up around it.\[^{[19]}\]

Mesoderm under the influence of the hypothalamus accumulates on both sides of the pouch, further inducing its development. At 37 days gestation, the neurohypophysis grows out from the infundibular recess and folds influenced more by rapid growth in the area around the tissue than by mitotic activity within it. The connection of the adenohypophysis is severed in the seventh week by cartilage growth of the sphenoid and vertebral body duplication.

The prechordal plate has previously been shown to induce the development of the hypophysis; the adenohypophyseal plate is in early contact with the prechordal plate directly. The initial signaling in the induction is thought to be through homeobox factors.\[^{[31]}\] BMP4 and FGF8 from the ventral forebrain are the second step in induction required for definitive development of the adenohypophyseal pouch.\[^{[5]}\] When the plate is replaced by notochord, contact is retained with the early glandular structures. Early secretion of sonic hedgehog (SHH) from the notochord triggers further development of the gland.\[^{[29]}\] Additional SHH from neural ectoderm up regulates pituitary specific genes, specifically pitx3.\[^{[10,31]}\] Once the pituitary placode has been induced, further patterning is induced by SHH from the oral ectoderm. Excess SHH signaling has been shown in zebra fish to lead to a widened gland. Lack of SHH leads to pituitary agenesis. Ectopic signaling after plate induction has not been shown to induce duplicate structures.\[^{[10,26]}\] Thus, an early developmental insult must be present to create DPG.

**Duplication of the pituitary gland**

Duplication of organs can arise from several developmental errors. Organs that form from two separate primordia may be duplicated from a failure of fusion. Those that form as a single entity require either a specific insult or a second induction signal to create duplication. Since the pituitary is formed from a single primordium, induction or insult must be considered when examining the cause of hypophyseal duplication.

Previously proposed theories for DPG include failed twinning,\[^{[1,22]}\] teratogens,\[^{[18]}\] and an extreme form of the median cleft face syndrome.\[^{[8,13,16]}\] Twinning will generally involve the entire face instead of focusing on the lower aspect, a specific teratogen has yet to be consistently identified, and the defects extending into the brain in this patient with a duplicate ventricular system and circle of Willis argue against an extension of the median cleft face theory. The distinct conglomeration of attributes seen in this, and most, DPG patients suggests another explanation – these characteristics seem to fall into a spectrum of defects that may be explainable by implicating early blastogenesis.\[^{[29]}\]

Morton (1956) proposed that DPG and the associated cranio-facial abnormalities could be explained by splitting of the notochord or prechordal plate at its rostral end. This would lead to the duplicate facial structures, such as bifid tongue, bifid uvula, supernumerary teeth, and nasal/palatal clefting observed in most cases of pituitary duplication; 22 of the 40 cases reviewed
demonstrated midfacial defects [Table 1].

Since the notochord induces formation of the pituitary plaque, a split notochord of prechordal plate would also lead to duplication of the hypophysis. Midline signaling defects, later in the process that cause clefting or other facial abnormalities would be unlikely to include hypophyseal duplication, as duplication must occur in the initial stages of formation.

Failed twinning was first proposed as an explanation of DPG by Ahlfeld in 1880. It is hypothesized that two notochords are formed but remain in too close proximity to develop separately, leading to conjoined twins.[1,22] Other authors argue that an incomplete split in the embryo between the 13th and 25th gestational day causes the malformation.[14] The distinction between a focal duplicative process versus a second complete notochordal axis that would represent true twinning is often difficult to discern.[14,36] The observations that only one spinal cord is present, the lack of duplication of brainstem structures and the confinement of neural defects to the forebrain leads us to believe that this case of DPG is not due to failed twinning but rather a focal defect.

Another term that bears mention is diprosopus — defined as two faces with one head and one body.[14] This term is often applied to patients with facial defects and can range from mild widening of the facial bones to complete duplication of all facial structures including eyes.[36] Only 37 cases of complete fetal diprosopus have been reported, with only one living past the fetal stage.[14] Wu reports a single case of diprosopus that was found to have DPG; in his case, as in the one presented here, the cause is believed to be a bifurcation at the rostral tip of the notochord rather than a complete duplication that would represent failed twinning.[16] The current case report closely resembles infants with diprosopus, but differs in that the duplication is present in only part of the face. Furthermore, a high rate of anencephaly and hence, the rate of morbidity and mortality is well known to be associated with diprosopus.

The authors believe that a focal defect causing a split notochord could best explain the abnormalities described in our patient. As the notochord induces brain development, the duplicate ventricular system, circulation and additional cerebral peduncle could be explained by a notochord split extending further caudally. Involvement of the cervical vertebrae suggests an extensive split occurring early in blastogenesis.

**Spectrum of blastogenesis defects**
Most cases of DPG are associated with hypothalamic thickening on MRI. This finding has alternately been interpreted as hypothalamic hamartoma or duplication of hypothalamic nuclei.[21] The association with DPG...

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**Table 1: Duplication of the pituitary gland and duplication of the pituitary gland-plus syndrome**

| Clinical Findings | Authors( year) |
|-------------------|-----------------|
| DPG + cleft lip/palate (CL/P)* | Ahlfeld (1880),[1] Giroud (1959)[12] Vieira (2007)[34] |
| DPG + duplication of basilar artery (DBA)** | Bainborough (1958),[6] Burke (2000),[6] Rylas (1993)[25] |
| DPG + absent corpus callosum (ACC) | de Penna – cases 1 & 2 (2005),[38] Lam (1999) |
| DPG + spinal column defects (SCD)** | Shroff – case 1 (2003)[38] |
| DPG + CL/P + NPT (nasopharyngeal teratoma) | Il’ina (1989),[17] Bale – case 2 (1976)[15] |
| DPG + CL/P + bifid tongue/uvula (BT/U) | Roessmann (1985)[42] Slavotinek – case 2 (2005)[36] |
| DPG + CL/P + SCD | Hamon-Kerautret (1998),[10] Shah (1997)[27] |
| DPG + CL/P + DBA | Morton (1957)[2] Vittore (2005)[25] |
| DPG + CL/P + ACC + BT/U | Bacsich (1964)[21] |
| DPG + CL/P + SCD | Knic (2009)[20] |
| DPG + CL/P + DBA | Bale – case 1 (1976)[30] Tagliavini (1986)[30] |
| DPG + CL/P + ACC + SCD | Hori (1983),[18] Mutiu (2004)[23] |
| DPG + CL/P + ACC + SCD + BT/U | Bagherian (1984),[13] Wu 2002[31] |
| DPG + CL/P + NPT + BT/U | Kollias (1995),[16] Slavotinek – 1 (2005)[29] |
| DPG + CL/P + NPT + DBA | Uchino (2002)[32] |
| DPG + CL/P + NPT + SCD | Clausnitzer (1956),[11] Feller (1931),[11] Vandenhaute (2000)[33] |
| DPG + CL/P + NPT + SCD + BT/U | Slavotinek – case 3 (2005)[30] |
| DPG + DBA + NPT | Shroff – case 3 (2003)[28] |
| DPG + DBA + NPT + SCD | Shroff – case 4 (2003)[28] |
| DPG + DBA + NPT + ACC | Shroff – case 5 (2003)[28] |
| DPG + CL/P + DBA + NPT + ACC + SCD + BT/U + clival encephalocele | current report |

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*Chieft lip/palate includes one case of nasal clefting. **Duplication of the basilar artery includes cases described as partial duplication and “extreme fenestration” of the artery. ***Spinal column defects include splitting, duplication or clefting of the cervical or thoracic vertebrae as well as myelomeningocele.
and precocious puberty has been reported previously and hypothesized to be affected by the accompanying hypothalamic malformations.[9] In cases where autopsy has been possible, there have been reports of hypothalamic hamartoma and pseudohamartoma.[10,11] It is likely that the incidence of hypothalamic hamartomas may be higher than current evidence demonstrates due to diagnostic and reporting issues; many authors have not included an assessment of the hypothalamus in previous reports. One previous report of triplication of the hypophysis exists; the patient displayed a third midline gland with separate stalk that was incompletely developed.[21]

The patient presented displays the most extensive collection of clinical features associated with DPG reported to date [Table 1]. Additionally, a midline fusion defect in the clivus with associated encephalocele is present; to the best of our knowledge there has been only one previous report of an isolated clival encephalocele by Kaptain et al. (2000).[18] The severity of intellectual dysfunction in this patient is also unique; in the DPG patients that live past childhood most retain normal intellectual functioning.[23,29,34] The extensive spectrum of developmental malformations seen in this patient and cortical brain involvement is likely the explanation for her intellectual disability.

While bifid tongue is a commonly associated feature with DPG, most patients present with a common tongue base with a distal split. In the current case report, the split in tongues continues through the base. The two separate tongues are able to move volitionally and independently [Figure 1b]. These characteristics lead us to call this feature a double tongue, instead of a bifid tongue, which has not been previously reported.

The only other feature that has been repeatedly associated with DPG is congenital diaphragmatic hernia (CDH) in 5/8 previous cases.[2,11,17,29,30] To date, no theory has been proposed linking CDH with DPG; splitting of the rostral tip of the notochord would be unlikely to cause defects at the level of the diaphragm.

Etiology
Analysis of the patient’s blood was performed by microarray-based comparative genomic hybridization which is designed to identify DNA copy number gains and losses. The probes are spaced every 35kb throughout the genome with one probe every 10kb in regions known to have clinical significance. Genomic imbalances less than 100kb may not be detected. This test does not detect point mutations, small deletions or duplications within genes. The result of analysis of 3,397 loci using oligonucleotide probes did not detect any significant copy number abnormalities in the patient’s DNA.

Genetic control of the notochord’s influence on embryonic development is poorly understood in humans.

Since microarray comparative genomic hybridization is a newer test, the majority of previously reported cases have not undergone such testing. While the current evidence supports an early notochordal split as explanation for the malformations observed in this patient, the cause of the split remains unknown. One possibility may be interference from the tumor causing mechanical obstruction leading to notochordal splitting around the mass, but it is difficult to determine if the teratoma was present at an early enough stage to influence development.

CONCLUSIONS
Duplication of the pituitary gland (DPG) appears to arise from blastogenesis defects. Splitting of the rostral end of the notochord can be used to explain the spectrum of malformations seen in these cases. The current report elucidates the broadest range of defects reported to date with the addition of a clival encephalocele, third cerebral peduncle, duplication of the odontoid process and double tongue. Considering the fact that DPG is uniquely present in the spectrum, we propose that these defects occur as part of a syndrome continuum that may be termed as DPG-plus syndrome.

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