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Duplication of Pituitary Gland-plus Syndrome presenting with a Transcranial Dermoid Cyst

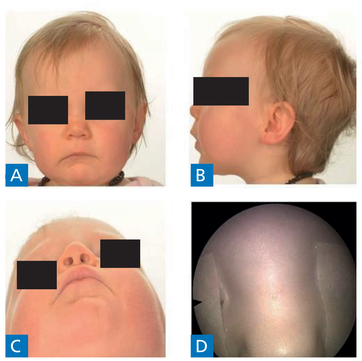
Purpose of this case report

- To promulgate the clinical presentation and Multi-disciplinary team management of a very rare and complex craniofacial malformation- **DPG-plus syndrome**
- To review the endocrine complications associated with this syndrome

Case report

- A term new-born female was found to have **a cleft palate and an unusual lump on the dorsum of tongue by her mother on day 1 of life**
- Antenatal History: Intrauterine fetal growth retardation during 3rd trimester of pregnancy
- Birth Weight: 2.98 Kilograms (9th percentile)
- Ethnicity: Caucasian
- Family: non consanguineous marriage, no h/o any significant illness except that her father was born with Gastroschisis
- **Day 9 of life:** re-admitted acutely with difficulty in feeding and obstructive breathing
- Stertor, tracheal tug and cyanosis in supine position
- Examination by Cleft palate surgeon
- **Cleft palate appearance was highly unusual (wide u-shaped cleft approximately 17 mm defect and a bifid Uvula), with a large nasopharyngeal mass partly filling the defect and**
- A high ridged large tongue and a soft tissue mass on the tongue dorsum
- She also had soft dysmorphic features like hypertelorism, low set ears, micrognathia
- A small dimple and sinus on nasal bridge with hair protruding out of it
- Cardiovascular, respiratory, abdominal, spine, neurological and limb examinations were normal
- **Initial Management:**
  - Referral to the Cleft palate team
  - Nursed in 30 degrees upright position at home and slept on an apnoea mattress

Facial features and nasal pit demonstration

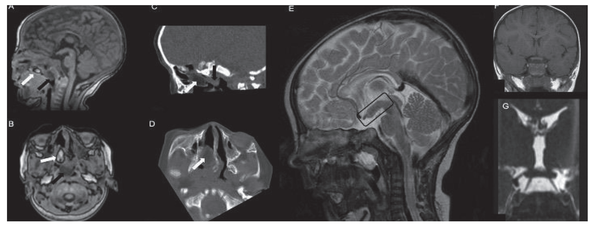


Age -15 months
A to C showing hypertelorism, low set ears and micro-retrognathia
D - picture taken during endoscopic procedure demonstrating her nasal pit

Radiological Findings

- **At five months of age:**
  - Underwent craniofacial and brain Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) scan, which revealed
  - A duplicated pituitary gland
  - Both anterior and posterior elements of pituitary gland were duplicated with separate infundibulae
  - Thickening of floor of third ventricle (hypothalamic hamartoma) in continuity with the anterior aspect of the midbrain, with mamillary bodies not being separately identified (tubomamillary fusion)
  - Duplication of basilar artery, broad flat Sella and cleft in odontoid peg
  - A large right nasopharyngeal teratoma
  - A trans cranial nasal dermoid sinus and cyst extending from external nose, through the nasal bones and through the frontal region to just above cribriform plate
  - CT scan of skull base confirmed the midline cranial osseous defect.
- **She was suspected to have DPG-plus syndrome**

Craniofacial MRI scan at five months of age



Referrals and Results

1) **Paediatric neuro-oncology Multi-Disciplinary Team (MDT)** meeting and assessment by craniofacial team(maxillofacial, plastic and neurosurgery): possibility of Double Pituitary Gland-plus (DPG-plus) syndrome as the likely diagnosis.
- The following results were obtained:
  a) **Baseline pituitary function tests** including TSH, free T4, early morning Cortisol and IGF-1, which were within normal limits
  b) **Germ cell tumor markers** total HCG < 5 u/l (normal), AFP 112 ku/l (within normal limits for a chronological age of 6 months)
2) **Involvement of Geneticist and CGH array testing:** CGH showed a DNA copy number variant 16q23 0.2MB, not known to be related to DPG-plus syndrome
3) **Cleft Lip and Palate service:** monitored feeding and provided support to the family
4) **Ear, Nose and Throat:**
   - Nasendoscopy: large right nasopharyngeal mass
   - Bilateral serous otitis media
   - Overnight oximetry and Transcutaneous carbon di-oxide (TOSCA) study: Normal

Surgical Management

1) **Resection of nasopharyngeal mass at 8 months of age, in view of progressive airway obstructive symptoms and cyanosis in supine posture**
- Histopathology revealed the nasopharyngeal mass to be a mature benign teratoma and the tongue polyp, a hamartoma
- 2 months post-op: breathing and feeding significantly improved

2) **Cleft palate repair at 15 months of age - modified Von Langenbeck repair method**
- 1 month Post-operatively - noted to have good repair except for a fistula within the mid-posterior third of the hard palate - plan made for an elective closure in future

3) **Trans-cranial dermoid cyst and nasal pit resection was performed at 27 months of age, in view of**
- Progressive transcranial extension of the nasal dermoid from its superficial dermal opening to the falx intracranially, and an increase in the lesion's overall size
- Histologically, dermoid cyst was lined by keratinised squamous epithelium and contained adnexal structures with no evidence of malignancy
- Post-operative MRI scan confirmed that complete resection was achieved

Growth and Development

- **At 3 years of age;**
  - This child has normal growth, development and neurological examination and significant improvement in speech (with speech and language therapy)
  - Her weight is tracking between the 50th -75th centile, length is tracking along 25th centile and head circumference is between 98th-99.6th centiles

Endocrinology

- Baseline endocrine tests including LH, FSH, Estradiol, morning cortisol, thyroid function tests, IGF-1 and serum osmolality performed **at 7 months, 16 months and again at 27 months of age are within normal limits**

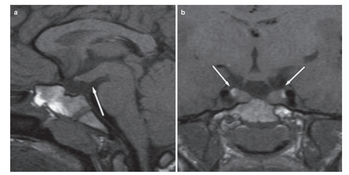
Follow-up Plan

- She remains under c**ontinued MDT surveillance and is planned to have annual surveillance Craniofacial MRI scans**, due to risk of recurrence of teratoma and association of precocious puberty with hypothalamic hamartoma

Duplicated pituitary gland-plus syndrome

- Duplication of pituitary gland in association with other midline craniofacial anomalies - also described as "DPG-plus syndrome "- is an extremely rare developmental anomaly with only 52 cases reported worldwide so far
- Proposed pathogenetic mechanism (Morton's theory): splitting of rostral notochord and prechordal plate during blastogenesis

Atlas of Sellar and Parasellar Lesions, Clinical, Radiologic, and Pathologic Correlations, 497-499, 2016



- **DPG's most frequent associations:**
  - Hypertelorism
  - Cleft lip and/or palate
  - Hypothalamic anomalies
  - Sellar malformations
  - Naso-oro-pharyngeal tumours
  - Spinal defects
  - Corpus callosum malformations
  - Bifid tongue or uvula
  - Basilar artery anomalies

Endocrine manifestations of DPG-plus syndrome

- **Central Precocious Puberty (CPP) is** the most common reported endocrine manifestations in association with DPG-plus syndrome
- Delayed puberty and secondary hypogonadism are other pituitary hormone abnormalities that have been reported in a few cases
- Of the 40 cases reported till 2011, 11 female children survived beyond infancy and 7 of these female children developed CPP
- The exact mechanism for development of CPP in these patients is still unknown.
- Interruption of lateral cell migration and possible duplication of hypothalamic nuclei with resultant tubomamillary fusion has been hypothesized as a possible mechanism
- Treatment with Gonadotropin releasing hormone analogs has been reported to be successful and causes arrest of further pubertal progression

Case significance

- This case report adds significantly to the growing body of literature on the clinical presentation and complex management of children with DPG-plus syndrome
- This patient is also the **first** reported case of DPG syndrome with a **nasal dermoid and intradural extension of the dermoid**

References

1. Giovanni Prezioso, Madelenna Petroroli, Michela Bergonzani et al.Duplication of the Pituitary Gland (DPG)-Plus Syndrome Associated With Midline Anomalies and Precocious Puberty: A Case Report and Review of the Literature. Front endocrinol. 2021; 12: 685888.
2. Manjila S, Miller EA, Vadera S, Goel RK, Khan FR, Crowe C, et al. Duplication of the pituitary gland associated with multiple blastogenesis defects: Duplication of the pituitary gland (DPG)-plus syndrome. Case report and review of literature. Surg Neurol Int. 2012;3:23.
3. Slavotinek A, Parisi M, Heike C et al. . Craniofacial defects of blastogenesis: duplication of pituitary with cleft palate and oropharyngeal tumors. Am J Med Genet A 2005;135:13–20
4. De Penna GC, Pimenta MP, Drummond JB et al. Duplication of the hypophysis associated with precocious puberty: presentation of two cases and review of pituitary embryogenesis. Arq Bras Endocrinol Metabol. 2005;49:323–7
5. Vieira TC, Chinen RN, Ribeiro MR et al . Central precocious puberty associated with pituitary duplication and midline defects. J Pediatric Endocrinol Metabol. 2007,20:1141–1144
6. Akin, Leyla; Kendirci et al. Pituitary duplication: a rare cause of precocious puberty. Child's Nervous System, 2011, 27 (7), pp.1157-1160
7. PENNA, Gustavo Cancela et al. Duplication of the hypophysis associated with precocious puberty: presentation of two cases and review of pituitary embryogenesis. *Arq Bras Endocrinol Metab* .49, n.2
8. Burke M, Zinkovsky S, Abrantes MA et al. Duplication of the hypophysis. **Paediatric Neurosurgery**. 2000, 33, pp95-9.