J. Fetal Med. (March 2021) 8:65–70
https://doi.org/10.1007/s40556-020-00283-2

BRIEF COMMUNICATION

Prenatal Binder Phenotype: Physician's Dilemma-A Case Report

Ashutosh Gupta[1] · Anjila Aneja[2] · Neena Bahl[2] · Rupam Arora[3] · Renu Raina Sehgal[4] · Pankaj Saini[5]

Received: 7 July 2020 / Accepted: 28 November 2020 / Published online: 3 January 2021

Abstract The Binder phenotype is defined by midface hypoplasia, underdeveloped frontal sinuses, hypoplastic and abnormally positioned nasal bones, nostrils appearing moon or comma-shaped and prognathism. It is heterogeneous in etiology and not fully understood. Multiple causative factors are described. The physician's dilemma is of diagnosing the fetal abnormalities on antenatal ultrasound for which there is no confirmatory testing. There are management and ethical problems regarding the diagnosis, further investigations and confirmation of the diagnosis. The Binder phenotype is a clinical diagnosis with multiple differential diagnoses. It carries an uncertain and unpredictable course and prognosis which might be difficult for both clinician and parents to predict and comprehend. Genetic counseling has to be variable depending upon the diagnosis.

Keywords Binder phenotype · Midface hypoplasia · Uncertain · Unpredictable course · Genetic counseling · Chondrodysplasia punctata teratogens

✉ Ashutosh Gupta
dr_ashutosh75@rediffmail.com

Anjila Aneja
anjilaaneja1966@gmail.com

Neena Bahl
drneenabahl9@gmail.com

Rupam Arora
rupam.arora@gmail.com

Renu Raina Sehgal
renus@artemishospitals.com

Pankaj Saini
drpankajsaini@gmail.com

[1] Foetal Medicine and Medical Genetics, Artemis Hospitals, Sector 51, Gurgaon 122001, India

[2] Department of Minimal Access Surgery (Gynecology), Fortis Memorial Research Institute, Gurgaon, Sector 44, Gurgaon 122001, India

[3] Department of Obstetrics and Gynecology, Max Balaji Hospital, 108 A, Indraprastha extension, Patparganj, New Delhi 110092, India

[4] Department of Obstetrics and Gynecology, Artemis Health Institute, Sector 51, Gurgaon 122001, India

[5] Department of Radiology, Manipal Hospitals, Sector 6, Dwarka, New Delhi 110075, India

Introduction

Binder phenotype is a rare congenital anomaly characterized by midface hypoplasia, particularly of maxillonasal region with an abnormally short, flattened nose. The use of the term Binder phenotype has been recommended rather than Binder syndrome [1]. The Binder phenotype was first described by Binder in 1962, with distinctive facial features [2].

The characteristic facial features were delineated in detail by Keppler-Noreuil and Wenzel; they summarized six features namely, an arhinoid face, abnormal nasal bones, intermaxillary hypoplasia, hypoplastic anterior nasal spine, atrophy of nasal mucosa, and hypoplastic frontal sinus [3].

The pathognomonic features of Binder phenotype are midface hypoplasia, underdeveloped frontal sinuses, hypoplastic and abnormally positioned nasal bones, flattened nasal bridge, abnormally short columella with nostril appearing moon or comma-shaped with prognathism leading to malocclusion.

Associated abnormalities include a vertebral anomaly, hearing impairment, cleft palate, strabismus, congenital cardiac defects and intellectual disability. The specific clinical symptoms and their severity are variable depending upon the underlying anatomical abnormalities.

This is a clinical diagnosis with multiple differential diagnoses which carries an uncertain course and unpredictable prognosis. This may be difficult for clinicians and parents to comprehend. It is usually isolated but may be associated with other anomalies and developmental disorders.

Etiology

This is heterogeneous and not fully understood. This include: causative categories described [4–6]:

1. Teratogenic/Environmental factors
    - Birth trauma,
    - Warfarin embryopathy and other vitamin K deficiencies (Vitamin K epoxide reductase deficiency),
    - Maternal exposure to phenytoin, rubella,
    - Maternal autoimmune disease (systemic lupus erythematosus [SLE], mixed connective tissue disease and scleroderma),
    - Maternal anticoagulation,
    - Disorders associated with decreased first-trimester Vitamin K levels (hyperemesis gravidarum, biliary lithiasis, pancreatitis, hepatic disease and alcoholism).
2. Chromosomal (Xp22.3 deletion)
3. Single gene disorders
    - Autosomal recessive chondrodysplasia punctata,
    - Brachytelephalangic chondrodysplasia punctata,
    - Conradi-Hunermann syndrome,
    - Keutel syndrome,
    - Stickler syndrome,
    - Robinow syndrome,
    - Infantile sialic acid storage disorder.

The defect is largely sporadic. However, familial occurrence has been reported possibly in an autosomal dominant manner. Some authors believe that Binder type nasomaxillary dysplasia may be a milder variant of chondrodysplasia punctata (CDP). In a large case series of 9 prenatally diagnosed Binder phenotype, all were found to be chondrodysplasia punctata [7]. A CDP has a characteristic stippled epiphyses; affecting both males and females equally with the prevalence of less than 1 per 10,000 live births. Many go undiagnosed.

Case Report

We have had an experience of 2 antenatal cases presenting at around 29 weeks of gestation. Both of them were primigravida with no high risk factors (congenital syphilis, rubella infection, autoimmune disease, anticoagulation, antiepileptic therapy) that seemed responsible for the causation of the binder phenotype.

Fetal biometry was within normal limits. There was no evidence of rhizomelic shortening, craniosynostosis or abnormal genitalia. There were no obvious major or minor soft markers for common aneuploidies and the maternal serum screening for aneuploidy was also low risk for common aneuploidies.

Nasal bones were visualized, appeared to be small, fetal midface was seen hypoplastic, with an abnormal facial profile in sagittal view, an axial view also suggested the nasal tip to hypoplastic and depressed and 4D ultrasound showed that binder phenotype. (Fig. 1).

In case 2, 4D ultrasound delineated very clearly the element of midface hypoplasia, abnormal and depressed nasal tip with abnormal columella and abnormal nostril highly suspicious of binder phenotype. (Fig. 2).

As the diagnosis of a Binder phenotype was and is usually delayed as the fetal soft tissue and facial profile gets more defined at around 29 weeks (Fig. 3), the possibility of taking an irreversible decision in the Indian scenario is not feasible. Binder phenotype is a clinical diagnosis with multiple differential diagnoses (Table 1) which may have a very variable, uncertain and unpredictable course thus making any counseling very difficult for both clinician and parents.

Both patients were counseled regarding the varied etiology and respiratory difficulties in the immediate postnatal period. One of the babies had some respiratory difficulty in the immediate postnatal period but settled with time.

Further investigation for confirmation of the underlying etiology is not straight forward. A large number of tests are required to assess the etiology. Results of these tests may take 3–5 weeks.

It has been suggested in literature that the isolated Binder facial phenotype is most likely to be milder forms of chondrodysplasia punctata.

Investigations that Can be Done

Binder phenotype-related diagnostic testing includes:

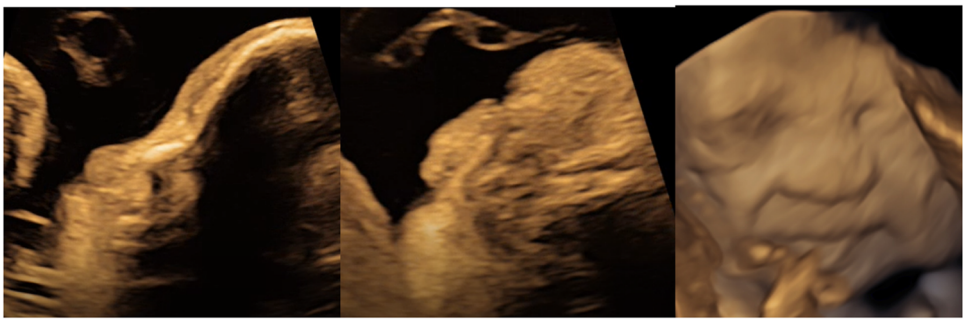

Fig. 1 2D and 4D antenatal ultrasound (Case 1) showed Binder phenotype. Midface hypoplasia, hypoplastic and abnormal nasal bones (2D sagittal view), abnormal nostril (2D axial view), flattened nasal bridge (4D), at 29 weeks of gestation

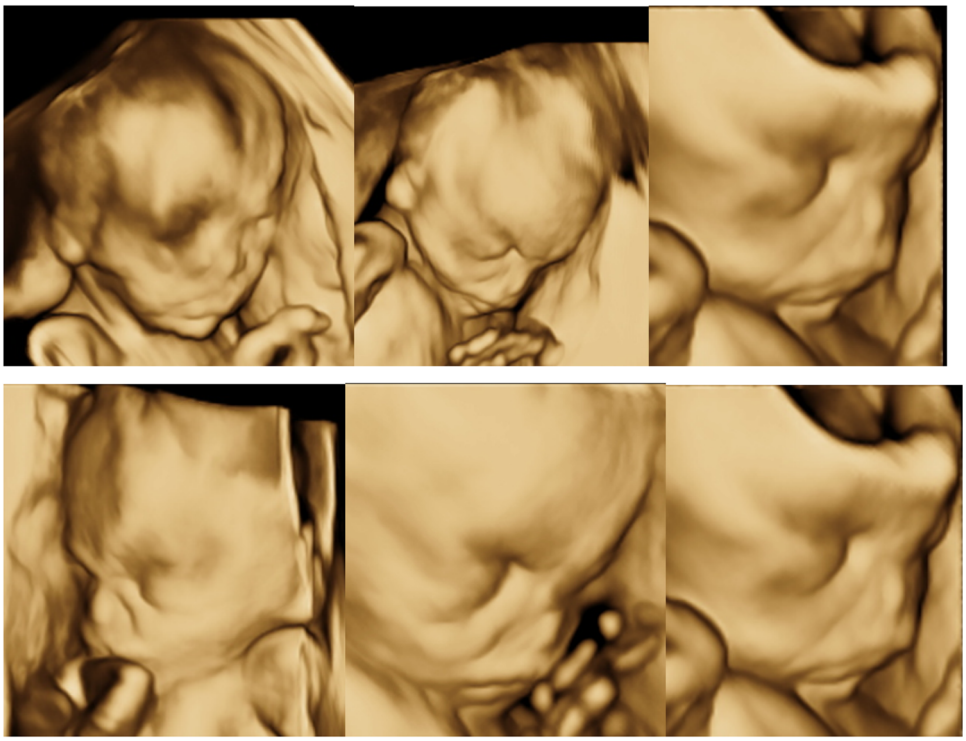

Fig. 2 Surface rendering 4D image antenatal ultrasound (Case 2) showing distinctive facial features for Binder phenotype. Midface hypoplasia, hypoplastic and abnormal nasal bones, flattened nasal bridge, abnormal columella at 29 weeks of gestation

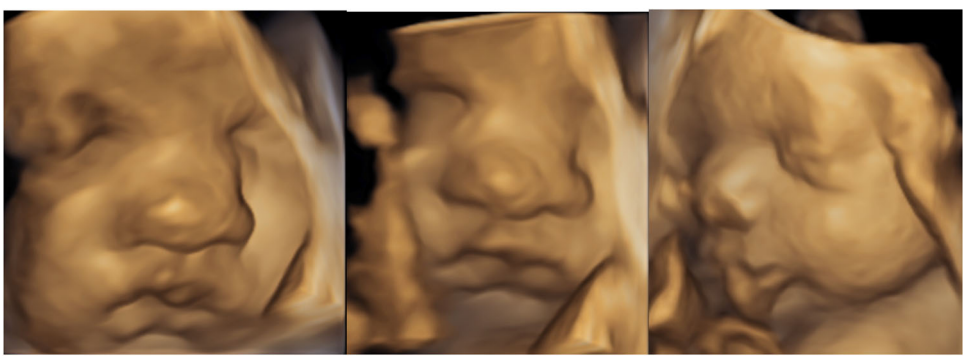

Fig. 3 4D antenatal ultrasound showing normal facial profile at 29 weeks of gestation (different patient—for comparison) depicting normally developed maxilla

1. Array comparative genomic hybridization for chromosomal abnormality.

2. Clinical gene sequencing for EBP gene (Chondrodysplasia punctata 2, X-Linked); PEX7 (Rhizomelic chondrodysplasia punctata Type 1); ARSL (ARSE) (Chondrodysplasia punctata 1, X-Linked); MGP (Keutel syndrome); PEX1,2,3,5,6,10,11B,12,13,14,16,19,26 (Zellweger spectrum disorder), COL2A1, COL11A1 (Stickler syndrome); DVL1, DVL3, WNT5A (Autosomal dominant Robinow syndrome); SLC17A5 gene (Sialic acid storage disease).

Table 1 Depicting multiple differential diagnosis of the primary finding of Midface hypoplasia; additional findings of the differential and causative gene with mode of the inheritance

Midface hypoplasia	Diagnosis	Additional findings	Inheritance
	Binder Syndrome OMIM 155050	Maxillonasal dysplasia, Malocclusion, Terminal phalangeal hypoplasia of hand, Vertebral clefting, Nasal hypoplasia, Hypertelorism	AD, AR
	Schinzel-Giedion syndrome OMIM: 269150	Hydronephrosis, skull anomalies, talipes and cardiac anomalies	De novo mutations, SETBP1 gene (18q21.1), gain-of-function or dominant-negative effect AD
	Crouzon syndrome	Variable multisuture craniosynostosis, nonsyndactyly, Vertebral fusions in 25% (C2–C3)	FGFR2 gene AD
	EEC (ectrodactyly–ectodermal dysplasia) syndrome	Cleft Lip, ectrodactyly (lobster claw anomaly of hands and feet) maxillary hypoplasia, long philtrum, choanal atresia	TP63 gene AD
	Chondrodysplasia punctate, X Linked OMIM: 302960	Cataract, symmetric rhizomelic limb shortening and epiphyseal calcifications	EBP gene (Xp11.23-p11.22) XL
	Chondrodysplasia punctate, Rhizomelic type OMIM 215100	Epiphyseal stippling, vertebrae irregularities, rhizomelia and short stature, talipes dysplastic external ears, and micrognathia, congenital contractures, characteristic ocular involvement, dwarfism, spasticity, ichthyosis and severe intellectual disability	Homozygous or compound heterozygous mutation in the PEX7 gene AR
	Chondrodysplasia punctata, tibia-metacarpal (OMIM 118651) and humero-metacarpal type	Shortening of the tibia / humerus, metacarpals and phalanges, Vertebral anomalies, CDP is confined to sacral, carpal, and tarsal areas	AD
	Robinow syndrome OMIM 180700	Ambiguous genitalia (micropenis in males or hypoplastic clitoris and labia minora in females), and characteristic facies resembling a fetal face, mesomelic limb shortening, renal and vertebral anomalies	WNT5A gene 3p14 AD
	Apert syndrome (acrocephalosyndactyly) OMIM 101200	Hypertelorism, turricephaly, macroglossia, syndactyly, fusion of cervical vertebrae, renal anomalies, and congenital heart disease	FGFR2 gene 10q26 AD
	Achondroplasia OMIM 100800	Rhizomelic shortening of the limbs, characteristic facies with frontal bossing and midface hypoplasia, exaggerated lumbar lordosis, limitation of elbow extension, genu varum, and trident hand, moderate macrocrania	FGFR3 gene 4p16.3 AD
	Thanatophoric dysplasia OMIM 187600	Thoracic hypoplasia, micromelia and cloverleaf skull	FGFR3 gene, 4p16 AD
	Chromosomal aneuploidies (Trisomy 18 and 21)		
	Drug and teratogen exposures Warfarin	Greatest risk period is approximately six to nine weeks post conception, midfacial hypoplasia and abnormally small nostrils. Growth retardation, intellectual disability, microcephaly, hearing loss, seizures, cataracts, corneal opacities	Teratogen
		Phenotypically similar to X-linked chondrodysplasia punctata 1, severe hypoplasia of the nasal bone (Binder anomaly), distal phalangeal abnormalities, and punctata of the axial skeleton	
	Foetal alcohol syndrome	Short palpebral fissures, epicanthus, smooth philtrum, long thin upper lip, microcephaly, corpus callosum dysgenesis, focal cortical thickening, hearing disorders, ear anomalies	Teratogen

Table 1 continued

Midface hypoplasia	Diagnosis	Additional findings	Inheritance
	Foetal Phenytoin syndrome	Hypertelorism, strabismus, ptosis, malformed ears, pterygium colli, microcephaly. Cleft lip / palate, underdeveloped fingers and toes, developmental delay	Teratogen

3. Post-squalene cholesterol biosynthesis; DHCR7 (Smith–Lemli–Opitz syndrome).

A postnatal skeletal survey may reveal epiphyseal stippling in the lower thoracic and lumbosacral spine, proximal femurs, pelvis, talus, and calcaneus. Spinal magnetic resonance imaging (MRI) may be required for narrowing of the foramen magnum, cervical vertebral and canal anomalies.

Management

As the disease is rare, there are no standardised management guidelines for the affected individual. Management depends on the underlying etiology, nature and severity of the disorder.

Chondrodysplasia Punctata may have punctate calcifications in the epiphyseal cartilage at the knee, hip, elbow, and shoulder joint which if extensive can involve hyoid bone, larynx, costochondral junctions and vertebrae. Calcification may also occur in the larynx, trachea, and main bronchi leading to stenosis and breathing difficulty. Vertebrae may be dysplastic or hypoplastic or show coronal or sagittal clefts. Cervical vertebral involvement may lead to cervical kyphosis, stenosis and atlantoaxial instability. Infantogram done in one of the patients did not demonstrate stippled epiphyses, emphasising the variable etiology (Fig. 4).

The Binder phenotype is at risk for several complications due to associated anatomical anomalies (sleep apnoea, mixed conductive and sensorineural hearing loss and cervical spinal stenosis/instability) [1]. As neonates are obligate nasal breathers; any obstruction in the upper airway can lead to significant respiratory distress, and may require tracheostomy [8].

Prenatal and perinatal care providers should be alerted for possible intubation in the immediate postnatal period and prolonged airway management. The management has to be a multidisciplinary and coordinated effort of a team of specialists; neonatologist, pediatricians, oral and plastic surgeons, craniofacial surgeons, orthodontists and orthopaedists. In some cases, cartilage grafting from the ribs is required to reconstruct the nose; more severe cases might require Le Fort I or II osteotomy [9].

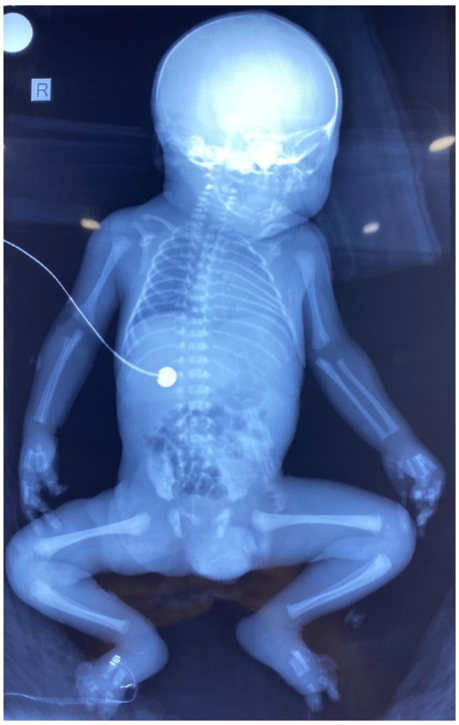

Fig. 4 Postnatal infantogram did not demonstrate stippled epiphyses (Common in Chondrodysplasia Punctata), emphasising the variable etiology for Binder Phenotype

Conclusion

The Binder phenotype is a clinical diagnosis with multiple differential diagnoses. It carries an uncertain and unpredictable course and prognosis which might be difficult for both clinician and parents to predict and comprehend. The dilemma is of diagnosing a fetal anomaly antenatally for which there is no confirmatory testing. There are management and ethical problems regarding the diagnosis and further investigations for confirmation of the

diagnosis. Genetic counseling is variable depending upon the diagnosis.

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