Bartsocas-Papas Syndrome: Case Report

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Abstract
Bartsocas-Papas syndrome (BPS) is a rare form of autosomal recessive disease, which is often severe and most of the time lethal. Only a few cases have been reported in the literature, so far mainly from the Mediterranean ancestry. We are describing here a case of severe form of BPS, which we encountered in our hospital in Dubai, UAE, which was diagnosed by antenatal scan; the baby had typical features of BPS and died immediately within few hours of life. Parents were first-degree consanguineous couples, and there was a family history of this disorder.

Introduction
Bartsocas-Papas syndrome (BPS) is an autosomal recessive form of popliteal pterygium syndrome (PPS). It is a very rare disease characterized by congenital craniofacial anomalies, popliteal webbing, and genitourinary and musculoskeletal anomalies. The condition is usually more severe and often lethal, and most of the affected patients die in utero or shortly after birth. It is often fatal in the neonatal period, but patients living until childhood have been reported [1]. The reported prevalence is <1/1,000,000. This condition was described in 1972 for the first time [2]. The gene involved is RIK4 – receptor interacting serine/threonine kinase 4. Mutations in RIK4 cause the autosomal recessive form of PPS [3]. This reported case had typical features of BPS, delivered at 34 weeks, and died soon after birth.

Case
A 32-year-old lady was referred to the Feto-Maternal unit in the second trimester of pregnancy for an antenatal evaluation of a congenitally abnormal fetus. She was an apparently healthy adult and had previous 3 deliveries. Two of the offspring had multiple congenital abnormalities. The first affected child was a female infant born at term and expired at the age of 9 months due to sepsis. She had severe craniofacial, limbs, and genital abnormalities. Genetic study confirmed a diagnosis of BPS (homozygous variant c.398A > G [p.H133R] was identified in the exon 2 of the RIK4 gene). The second child expired in utero at 7 months of pregnancy. All her pregnancies including the current pregnancy were spontaneous conceptions from the same consanguineous marriage.

In this pregnancy, the antenatal ultrasound revealed a small for gestational age fetus (below the fifth centile) with oligohydramnios and multiple congenital abnormalities including a midline cleft maxilla, absent right and left hands, bowed right and left femurs, absent fibulas, and absent right tibia. Antenatal microarray testing showed normal male pattern.

The mother was admitted to the hospital at 34 weeks of pregnancy with preterm labor and ruptured membranes. She delivered...
vaginally a 1,580-g male infant. The placenta was very small and calcified with a short cord. The baby was born hypoactive and bradycardic. The baby expired in the first hour of life. It had severe craniofacial abnormalities, pterygia of body joints (Fig. 1), ambiguous genitalia, imperforate anus (Fig. 2), and a dry thick skin (Fig. 3). Scalp hair, eyebrows, and eyelashes were absent. He had a narrow left palpebral fissure, right ankyloblepharon, and hypertelorism (Fig. 4). The nose was severely malformed with clefting (Fig. 4). Maxilla and mandibles were hypoplastic. There were no oral or nasal openings. Ears were large and low set. Forearm and metacarpal bones were short. Some metacarpal bones, all metatarsal bones, and all digits were absent (Fig. 5). Genetic testing confirmed a diagnosis of BPS. It showed pathogenic variant c.398 > G (p.H133R), and the RIPK4 gene was detected in homozygous state. The couple was informed about the preimplantation genetic diagnosis techniques and was advised to attend genetic counseling.

Discussion

BPS is a very rare congenital syndrome with autosomal recessive inheritance, variable expressivity, and incomplete penetrance. The 3 main clinical manifestations are craniofacial malformations (orofacial cleft, short palpebral fissure, ankyloblepharon, and hypoplastic nose), musculoskeletal anomalies (bilateral intracranial popliteal pterygia, bilateral popliteal webbing, and various digital deformities like syndactyly), and genitourinary anomalies (cryptorchidism, testicular agenesis or scrotal clefts, and inguinal hernia). There can be widely variable degrees of manifestations with which those carrying the mutation may be affected [4]. Almost all affected babies die in utero or infancy [1, 5]. This reported case from Dubai, United Arab Emir-}

Fig. 1. Severe bilateral webbing splinting shoulders, arms and mid forearm to anterior chest, and syndactyly of both hands.

Fig. 2. Ambiguous genitalia and an imperforate anus.

ates, had severe craniofacial abnormalities, pterygia of body joints, ambiguous genitalia, imperforate anus, and a dry thick skin. Scalp hair, eyebrows, and eyelashes were absent. He had a narrow left palpebral fissure, right ankyloblepharon, and hypertelorism. The nose was severely malformed with clefting. Maxilla and mandibles were hypoplastic. There were no oral or nasal openings. The ears were large and low set. Forearm and metacarpal bones were short. Some metacarpal bones, all metatarsal bones, and all digits were absent. The mother had 2 previous babies affected with similar abnormalities, 1 baby died at 9 months of age and another was stillborn at 7 months of gestation. The genetic testing of both the babies showed the homozygous variant c.398A > G [p.H133R] in the RIPK4 gene, confirming BPS. Mothers’ genetic testing revealed that she is a heterozygous carrier of the familial RIPK4 variant. A few authors from different countries have reported BPS cases with similar features and various manifestations [1, 4–6]. A case study [5] reported on 4 Arab sibs with manifestations of this syndrome and also had some additional traits that included cutis aplasia, widely spaced nipples, low-set umbilicus, and unilateral renal hypoplasia. In this case study, 1 was stillborn, and the other 3 children lived 10–17 months. Parents were nonconsanguineous, derived from different Bedouin tribes in Qatar and the United Arab Emirates. In another case study from Turkey [6], the fetus had severe lower limb findings, classical facial features of the syndrome, but less severe upper limb involvement. BPS is fatal in the newborn period in most cases. However, cases of patients who lived until childhood...
have been reported [3]. Josh et al. [4] reported a 10-month-old boy with bilateral complete cleft lip and palate, abnormal scalp hair, an absence of both upper eyelids, choanal atresia, syndactyly of the third and fourth fingers of the right hand, agenesis fingers on the left hand, bilateral popliteal pterygia, bilateral talipes equinovarus, agenesis of the toes of both lower extremities, intercrural webbing, an absence of testis, and scrotal anomaly. Multistage surgical correction was performed for the multiple congenital malformations in this case.

Careful history taking including family history and clinical examination of parents is necessary in cases of BPS due to the variable grades of clinical manifestations including various craniofacial anomalies, musculoskeletal anomalies including popliteal webbing (90%), and different grades of genital anomalies. Differential diagnosis between BPS, PPS, and Van der Woude syndrome is difficult most of the time since these 3 entities may represent a contiguous gene deletion syndrome or allelic variants [4]. Management of the living BPS babies needs a multidisciplinary team of plastic surgeons, pediatric surgeons, otolaryngologist, geneticists, dentists, physical therapists, pediatric urologists, anesthetists, pediatrics, social workers, and speech therapists [4]. It is a herculean task to reconstruct all defects in a child with BPS. Using increasingly sophisticated resuscitation and supportive techniques, it is possible that more patients with BPS will survive beyond the neonatal period but sometimes repeated and often unsuccessful surgical procedures can cause diminishing quality of life for the child [1].

**Conclusion**

Almost all cases of BPS reported have involved dead intrauterine pregnancies. This reported case of BPS from Dubai, United Arab Emirates, was born alive but died after some time since it had severe anomalies.

Consanguinity is an important factor contributing to the preponderance of autosomal recessive genetic disorders among the Arab populations [7]. Awareness and education about the genetic disorders, premarital genetic counseling as well as family-oriented genetic counseling, preimplantation genetic diagnosis, and various methods of prenatal diagnosis can be used to decrease the prevalence of the genetic disorders in this region.
Statement of Ethics

Ethical approval was not required for this case report in accordance with the Dubai Scientific Research Ethics Committee policies. Informed written consent from the mother was obtained for publishing the case and all accompanied images.

Conflict of Interest Statement

The authors have no conflicts to declare.

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Author Contributions

F.N. contributed to study concept and is the senior author and the manuscript reviewer. S.F. contributed to writing – original draft preparation, editing, and writing. N.M. is the manuscript reviewer. S.B. contributed to data collection and writing – original draft preparation. All authors read and approved the final manuscript.

Data Availability Statement

All data/images generated or analyzed during this case report are included in this article. Further enquiries can be directed to the corresponding author.

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