Paediatr Croat. 2018;62:96-100
www.paedcro.com
http://dx.doi.org/10.13112/PC.2018.14

Pfeiffer syndrome type 2 – two cases from the Pleven Registry of Congenital Anomalies

Katya Kovacheva, Zornica Kamburova, Victoria Atanasova, Andrey Hristov

Pfeiffer syndrome is a rare autosomal dominant congenital disorder with the main features of acrocephalic skull, midfacial hypoplasia, syndactyly of hands and feet, broad thumbs and big toes. Three clinical subtypes (with different diagnostic and prognostic implications) have been identified. We report on two cases of Pfeiffer syndrome type 2 (one of them diagnosed prenatally and the other detected in the newborn), identified through screening for congenital defects as an activity of the Pleven Registry of Congenital Anomalies (member of EUROCAT). Case 1 was a male foetus from terminated pregnancy following prenatal diagnosis. Foetal morphology ultrasound in the 28th week of gestation revealed craniosynostosis, cloverleaf skull, flat face, exophthalmos, macroglossia, short ribs, deformed spine, and abnormally shortened limbs (micromelia). Clinical examination after birth confirmed the diagnosis of Pfeiffer syndrome type 2. Case 2 was a boy (born at term, 40th week of gestation) diagnosed with Pfeiffer syndrome type 2 at birth. Multiple malformations were presented including cloverleaf skull, craniosynostosis of coronal suture, midfacial hypoplasia, depressed nasal bridge, high palate, exophthalmos, down-slanted palpebral fissures, hypertelorism, low-set ears, short neck, broad and medially deviated thumbs and hallux, clinodactyly V, skin syndactyly of II-III toe, short thorax with sternal depression, and anal atresia. The patient died from respiratory distress syndrome on the ninth day after birth. Severe malformations, high mortality and problems in clinical management determine poor prognosis in most cases of Pfeiffer syndrome type 2. Early prenatal diagnosis in pregnancies with severe foetal malformations and poor prognosis gives parents more time and opportunities for reproductive choices.

Key words: Pfeiffer syndrome type 2; cloverleaf skull; registry of congenital anomalies; prenatal diagnosis

INTRODUCTION

In 1964, *Pfeiffer* (1) was the first to describe acrocephalosyndactyly syndrome, characterized by bicoronal craniosynostosis, midface hypoplasia, broad thumbs and great toes, and partial and variable soft tissue syndactyly. The type of inheritance is autosomal dominant with complete penetrance and variable expressivity related to the presence or absence of syndactyly and the degree of severity. Pfeiffer syndrome (PS) (OMIM 101600) was classified into three clinical subtypes by *Cohen* in 1993. Type 1 is a 'mild' form of the syndrome, with brachycephaly, midfacial hypoplasia, finger and toe deformities, and autosomal dominant pattern of inheritance. Type 2 main features are cloverleaf skull, elbow ankylosis, poor prognosis and early demise (usually sporadic cases). Type 3 has the same features as type 2, but without cloverleaf skull (2).

Molecular genetics has provided better understanding of the molecular basis of PS, which is due to mutations in fibroblast growth factor receptor 1 *(FGFR1-* 8p11.2-p11) or *FGFR2* (10q26) (3).

We report on two cases of PS type 2 (one of them prenatally diagnosed and the other one detected in the new-

* Medical University of Pleven, Pleven, Bulgaria

Correspondence to:
Katya Kovacheva, PhD, MD, Medical University of Pleven, Pleven, Bulgaria, e-mail: katiakovach@gmail.com

Primljeno/Received: 8. 11. 2017., Prihvaćeno/Accepted: 14. 5. 2018.

born), identified through screening for congenital defects as an activity of the Pleven Registry of Congenital Anomalies (member of EUROCAT).

CASE REPORTS

Case 1

It was the first monitored pregnancy in the mother. The parents (27-year-old mother and 37-year-old father) were healthy and non-consanguineous. Routine ultrasound examination in 28th week of gestation revealed polyhydramnios, and multiple foetal malformations were suspected. The woman was referred for foetal morphology ultrasound. The sonographic features described were craniosynostosis, cloverleaf skull, flat face, exophthalmos, macroglossia, short ribs, deformed spine, and abnormally shortened limbs (micromelia). The conclusion was: severe bone dysplasia incompatible with life, Crouzon or Pfeiffer syndrome. Based on the poor prognosis of the malformations, termination of the pregnancy was considered.

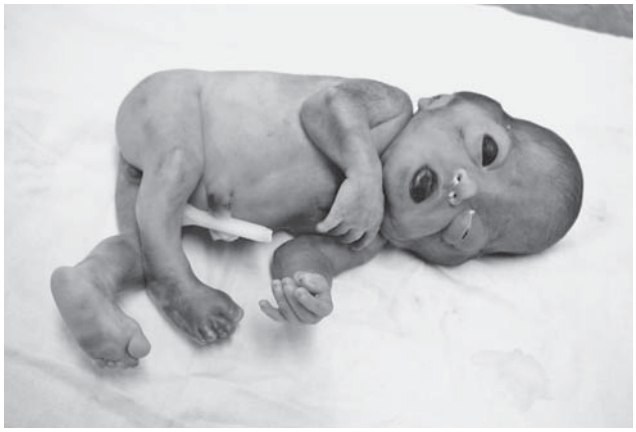

FIGURE 1.

A male baby was born (weight 1310 g, length 35 cm, cranial circumference 26 cm) and died 15 minutes after birth. Clinical examination revealed the following dysmorphological findings (Figure 1, Table 1): cloverleaf skull, coronal craniosynostosis, midfacial hypoplasia; exophthalmos, down-slanted palpebral fissures, hypertelorism; anteverted nares; low-set dysplastic ears; short neck; rhizomelic shortened limbs, broad and medially deviated thumbs, simian crease on both hands, broad big toes, skin syndactyly of II- III toes; spinal defects – scoliosis, defect with the characteristics of dermoid cyst with fistula in the sacral region and cryptorchidism.

Cytogenetic analysis of the foetus: 46,XY – normal male karyotype. Pathological examination did not find any addi-

TABLE 1. Clinical features of Pfeiffer syndrome (in the literature and in our cases)

Category	Subcategory	Clinical features in Pfeiffer syndrome [2,4]	Features in Case 1	Features in Case 2
Head and Neck	Head	Turribrachycephaly	–	–
		Clover-leaf skull (in some patients)	+	+
	Face	Maxillary hypoplasia	+	+
		Mandibular prognathism	–	–
	Eyes	Shallow orbits	+	+
		Hypertelorism	+	+
		Downslanting palpebral fissures	+	+
		Proptosis	+	+
		Strabismus	–	–
	Nose	Small nose	+	+
		Low nasal bridge	+	+
		Choanal atresia or stenosis	–	–
	Mouth	High-arched palate	–	+
	Teeth	Dental crowding	–	–
Respiratory	Airways	Cartilaginous trachea	–	–
		Laryngo-, tracheo-, bronchomalacia	–	–
Skeletal	Skull	Craniosynostosis (coronal with or without sagittal suture)	+	+
	Limbs	Radiohumeral synostosis of elbow	–	–
	Hands	Broad thumb	+	+
		Partial syndactyly of fingers and toes	+	+
		Brachymesophalangy of hands and feet	–	–
		Fifth finger clinodactyly	–	+
	Feet	Broad great toe	+	+
	Spine	Fused vertebrae	–	+
Neurologic	Central Nervous System	Occasional mental retardation	–	–
		Hydrocephalus	–	–
		Arnold-Chiari malformation	–	–
Other		Imperforate anus	–	+

tional malformations. Based on the clinical features Pfeiffer syndrome type 2 was diagnosed.

Case 2

A male baby was born after the first unmonitored and uneventful pregnancy of tze 17-years old healthy mother. The father was a 21-year-old healthy man. The baby was born after normal vaginal delivery at 40 weeks of gestation, weight 3450 g, length 50 cm, head circumference 35 cm. At birth, multiple malformations were found (Figure 2, Table 1): cloverleaf skull, craniosynostosis of coronal suture, midfacial hypoplasia, depressed nasal bridge, exophthalmos, downslanted palpebral fissures, hypertelorism, low-set ears, high palate, short neck; broad and medially deviated thumbs, clinodactyly of fifth fingers, broad and medially deviated bilateral hallux, skin syndactyly between the second and third toes; short thorax with sternal depression; and anal atresia.

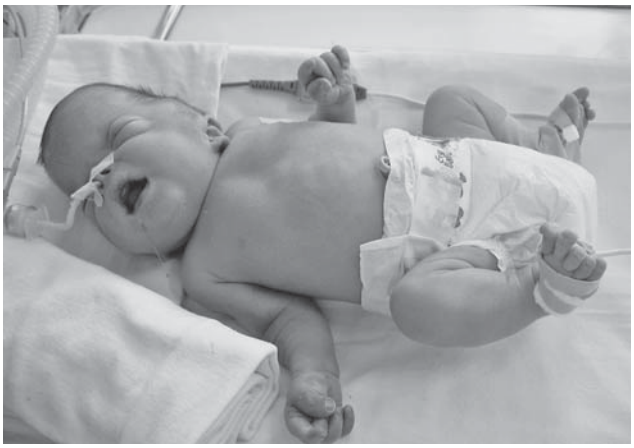

FIGURE 2.

On the second day after birth, the neonate underwent surgery for congenital anal atresia. The brain ultrasound scan found dilatation of frontal horns of lateral ventricles and hydrocephalus. Radiological findings were bilateral coronal craniosynostosis, hypoplasia of the mandible, maxilla and facial bones, short horizontal ribs, and fusion of thoracic vertebrae. The karyotype of the foetus was normal male 46,XY.

Based on the dysmorphological and radiological findings, the clinical diagnosis of Pfeiffer syndrome type 2 was established.

The baby developed respiratory distress syndrome and died on the ninth day after birth. Pathological examination confirmed the clinical diagnosis.

DISCUSSION

The real incidence of PS is unknown, but it is estimated to be 1 *per* 100 000 births (4). Three clinical subtypes (with different diagnostic and prognostic implications) have been identified. Severe ocular proptosis and early death are characteristics of PS types 2 and 3, whereas PS type 1 is a compatible with life and usually presents with midfacial hypoplasia without exophthalmia. Cloverleaf skull is a unique feature of type 2 (2, 5).

Usually, the diagnosis of PS is based mainly on the clinical phenotype and radiological findings. The differential diagnosis of PS includes the syndromes characterized by craniosynostosis, such as Apert syndrome, Carpenter syndrome, Crouzon syndrome, isolated cloverleaf skull, and thanatophoric dysplasia (Table 2) (5-9).

TABLE 2. **Differential diagnosis of Pfeiffer Syndrome (4, 5, 6)**

Disorder	Main Clinical Features	Cloverleaf Scull	Inheritance
Apert syndrome	Craniosynostosis, ocular proptosis, midfacial deficiency, syndactyly	Rare	Autosomal Dominant; most cases are sporadic
Carpenter syndrome	Craniosynostosis, preaxial polysyndactyly of feet, brachydactyly and clynodactyly with variable syndactyly of hands, congenital heart defects	Rare	Autosomal Recessive
Crouzon syndrome	Craniosinostosis, ocular proptosis, midfacial deficiency; no hand and foot anomaly	Uncommon	Autosomal Dominant
Pfeiffer syndrome	Craniosynostosis, ocular proptosis, midfacial deficiency, broad thumbs and great toes, variable soft tissue syndactyly of other digits	Common	Autosomal Dominant

Although PS and Apert syndrome (OMIM 101200) have some similarities, the two disorders appear to be nosologically and genetically distinct. In our cases, the lack of bone syndactyly (one of the major features of Apert syndrome) was the main reason to reject this diagnosis (2). Sometimes PS has been confused with Saethre-Chotzen (OMIM 101400) and Jackson-Weiss (OMIM 123150) syndromes, since broad toes may occur in both syndromes. Specific features of Saethre-Chotzen are triangular big toes, with bulbous shape and in valgus position. Broad big toes identical to those observed in PS may occur in some instances of Jackson-Weiss syndrome, although broad thumbs are never observed (6).

The trilobed skull deformity (cloverleaf skull) is a rare congenital anomaly that may be present as an isolated defect, but is usually part of an osteochondrodysplastic or dysostotic syndrome such as Apert, Crouzon (OMIM 123500) or PS (6). This anomaly has important prognostic implications because of the limited brain growth and eye exposure caused

by shallow orbits. The pathogenesis of the cloverleaf skull is unknown, but trilobed shape of the head, hydrocephalus and facial deformation have been attributed to intrauterine synostosis of cranial sutures. The abnormalities of cranial base may have played the role in respiratory distress in the baby reported.

The common clinical features of our two PS cases were cloverleaf skull, severe exophthalmos, midfacial hypoplasia, broad and medially deviated thumbs, broad big toes, and partial soft syndactyly between the second and third toes. Based on dysmorphological assessment of the main syndrome features and differential diagnosis between the three syndrome subtypes, the final diagnosis in our two cases was PS type 2 (Table 1) (2, 5, 10, 11).

Pfeiffer syndrome is an autosomal dominant disorder. The more severe type of the syndrome, PS type 2, is usually due to *de novo* mutations and the cases are sporadic. However, it is not possible to rule out the presence of mosaicism in one of the parents (in very rare cases). By molecular analysis, *Glaser et al*. proved that the origin of the mutations was paternal in all informative cases analysed. Advanced paternal age was noted for the fathers of patients with PS, compared with the fathers of control individuals (34.50±7.65 *vs*. 30.45±1.28 years, p<0.01) (12). Father's age (37 years) in Case 1 supports these findings. Low familial recurrence risk was considered in genetic counselling of the two affected families.

In our Case 1, the diagnosis of PS was made prenatally, during pregnancy monitoring by three-dimensional ultrasound (based on the specific head shape, anomalies of the face, hand and foot), while Case 2 was diagnosed in the neonate born to the mother with uncontrolled pregnancy. Severe malformations, high mortality and problems in clinical management/surgical correction determine the poor prognosis in most PS type 2 cases. Early prenatal diagnosis in pregnancies with severe foetal malformations and poor prognosis gives parents more time and opportunities for reproductive choices.

Acknowledgements

We thank Dr. Nikolai Slavov and Dr. Gabriela Tzankova (MHAT, AVIS-Medica, Pleven) for their assistance in the work on the Pleven Registry of Congenital Anomalies and providing clinical information concerning Case 2. The authors are grateful to Professor Dimitar Markov (MC, Markovs, Sofia) for dysmorphological expertise of foetus in Case 1.

NOVČANA POTPORA/*FUNDING*

Nema/*None*

ETIČKO ODOBRENJE/*ETHICAL APPROVAL*

Nije potrebno/*None*

SUKOB INTERESA/*CONFLICT OF INTEREST*

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SAŽETAK

Pfeifferov sindrom tip 2 – dva slučaja u Registru prirođenih anomalija u Plevenu, Bugarska

Katya Kovacheva, Zornica Kamburova, Victoria Atanasova, Andrey Hristov

Pfeifferov sindrom je rijetka autosomno dominantno nasljedna bolest, a glavna obilježja su akrocefalija, hipoplazija središnjeg dijela lica, sindaktilija šaka i stopala, široki palci i veliki nožni prsti. Postoje tri klinička podtipa Pfeifferova sindroma s različitim dijagnostičkim i prognostičkim implikacijama. Opisujemo dva slučaja Pfeifferova sindroma tip 2 (jedan dijagnosticiran prije rođenja i drugi otkriven u novorođenčeta) koje smo našli probirom na prirođene anomalije u Registru prirođenih anomalija u Plevenu (član EUROCAT-a). Prvi slučaj bio je muški fetus porođen nakon prenatalne dijagnoze. Ultrazvuk morfologije fetusa u 28. tjednu trudnoće otkrio je kraniosinostozu, lubanju nalik listu djeteline, spljošteno lice, egzoftalmus, makroglosiju, kratka rebra, deformitet kralježnice i kratke ekstremitete (mikromelija). Klinički pregled nakon rođenja potvrdio je dijagnozu Pfeifferova sindroma tip 2. Drugi slučaj bilo je muško novorođenče (rođeno u terminu, 40. tjedan trudnoće) kod kojega je Pfeifferov sindrom tip 2 dijagnosticiran pri rođenju. Utvrđene su višestruke malformacije uključujući lubanju poput lista djeteline, kraniosinostozu koronalnog šava, hipoplaziju središnjeg dijela lica, ulegnuti nosni hrbat, visoko nepce, egzoftalmus, spuštene vjeđe, hipertelorizam, nisko položene uške, širok vrat, široke i medijalno iskrivljene ručne i nožne palce, klinodaktiliju V, kožnu sindaktiliju nožnih prstiju II-III, kratak toraks sa sternalnom depresijom i analnu atreziju. Dijete je umrlo od sindroma respiracijskog distresa devetog dana nakon rođenja. Teške malformacije, visoka smrtnost i problemi u kliničkoj obradi određuju lošu prognozu u većini slučajeva Pfeifferova sindroma tip 2. Rana prenatalna dijagnoza u trudnoći s teškim malformacijama fetusa i lošom prognozom pruža roditeljima više više vremena i mogućnosti za reproduktivne odluke.

Ključne riječi: Pfeifferov sindrom tip 2, lubanja poput lista djeteline, registar prirođenih anomalija; prenatalna dijagnostika