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# Asymmetric Neonatal Crying: Microdeletion, Infection or Birth Injury? – A Case Report

Kornelija Koši-Šantić<sup>1</sup>, Dijana Rudan<sup>2</sup>, Damir Buković<sup>3</sup>, Jadranko Šegregur<sup>4</sup>, Jasenka Wagner<sup>5</sup>, Slavko Orešković<sup>3</sup>, Tomislav Župić<sup>3</sup> and Mirjana Radan<sup>6</sup>

<sup>1</sup> General Hospital Virovitica, Department of Paediatrics, Virovitica, Croatia

<sup>2</sup> University of Zagreb, University Hospital Dubrava, Department of Internal Medicine, Zagreb, Croatia

<sup>3</sup> University of Zagreb, University Hospital Center Zagreb, Department of Gynecology and Obstetrics, Zagreb, Croatia

<sup>4</sup> General Hospital Virovitica, Department of Gynecology and Obstetrics, Virovitica, Croatia

<sup>5</sup> »J.J. Strossmayer« University, School of Medicine, Cytogenetics Laboratory, Osijek, Croatia

<sup>6</sup> General Hospital Čakovec, Department of Gynecology and Obstetrics, Čakovec, Croatia

## ABSTRACT

*Asymmetric neonatal crying is a rare minor congenital abnormality caused by unilateral agenesis or hypoplasia of depressor anguli oris muscle and depressor labii inferioris muscle. It is either an isolated clinical finding or one of the clinical findings included in several malformation syndromes linked to a microdeletion within a chromosomal region 22q11.2. Some malformations in that region are associated with serious cardiovascular anomalies. Nowadays, standard diagnostic techniques for detecting aberrations within the chromosomal region 22q11.2 are fluorescence in situ hybridization (FISH) and multiplex ligation probe amplification (MLPA). This short report describes an eutrophic female newborn whose both lip corners are symmetrically positioned while at rest; while crying, left lip corner and left half of the lower lip are falling. She also has partial bilateral syndactyly between second and third toe, open foramen ovale and by ultrasound detected hyperechogenic region in the thalamus and brain parenchyme. Aiming to investigate etiopathogenesis of the newborn asymmetric crying and accompanying minor abnormalities, we have tried to verify or exclude: microdeletion syndrome, TORCH infection and birth injury. Recognising such a paresis soon after the delivery is of great importance and can be helpful in detecting other accompanying anomalies, especially cardiovascular anomalies.*

**Key words:** asymmetric neonatal crying, microdeletion 22q11.2, congenital malformation, TORCH, birth injury

## Introduction

Asymmetric neonatal crying or asymmetric crying facies (ACF) or congenital unilateral lower lip palsy (CULLP) are rare minor congenital anomalies but a different entity from congenital unilateral facial palsy (CUFP). It is caused by unilateral agenesis or hypoplasia of depressor anguli oris muscle (DAOM) and depressor labii inferioris muscle, muscles responsible for lower lip movements. It can be an isolated clinical finding or it can be coupled with other congenital anomalies, especially cardiovascular. Microdeletion syndromes (in general) can have variable phenotype consisting of a different combination of symptoms. It points out that in such a case, single genes whose mutations normally cause known monogenic diseases and anomalies, have lost their function<sup>1–3</sup>.

Microdeletions of a chromosomal region 22q11.2 are cause of different malformation syndromes such as Cayler syndrome, DiGeorge syndrome, Velocardiofacial syndrome Shprintzen, VACTERL association and CHARGE association. Those syndromes involve a wide spectrum of different single abnormalities but also have something in common. These common anomalies (facial anomalies, heart anomalies, aplasia or hypoplasia of thymus, hypoparathyroidism) are often seen in combination. The names of the particular syndromes are still in use, but a more general term, 22q11.2 deletion syndrome, encompasses the clinical spectrum to include the variable and numerous abnormalities (more than 180) in these people. The 22q11.2 deletion is possibly one of the most common

chromosomal disorders in humans; it has been estimated to range from 1:4000 to 1:10000 live births<sup>4-7</sup>.

At present, a routine diagnostic procedure for detecting aberration of the 22q11.2 chromosomal region include chromosome analysis by GTG-banding followed by either: a) fluorescence in situ hybridisation (FISH) or b) multiplex ligation-dependent probe amplification (MLPA). FISH is nowadays slowly being replaced by MLPA because MLPA is a faster and cheaper method for detecting chromosome deletions and duplications<sup>8</sup>.

### Case Report

Here we present a female eutrophic newborn born from a second pregnancy. The mother was hospitalized at the 15th week of gestation and treated with a progesteron because of retrochorial haematoma and bleeding. The newborn was vaginally delivered at the 41<sup>st</sup> week of gestation, with birth weight 3320 g, birth length 50 cm, head circumference 35 cm and vitality score according to Apgar 9, 10.

Examination after the delivery showed: normally configured head, anterior fontanel measuring 2 × 2 cm, both lip corners symmetrical at rest, left lip corner and left half of the lower lip falling while crying (Figures 1 and 2),



Fig. 1. Newborn facial symmetry while at rest.



Fig. 2. Newborn facial asymmetry while crying.



Fig. 3. Partial bilateral syndactyly between second and third toe of the left foot.



Fig. 4. Partial bilateral syndactyly between second and third toe of the right foot.

partial syndactyly of the second and third toe (Figures 3 and 4) of both feet (more distinct on the right foot), normal neurological and somatic status and gestational age of 40 weeks (according to Petrucci). The child had transient newborn hypoglycaemia (blood glucose 2.2 mmol/L) and physiological newborn jaundice (bilirubin 139 μmol/L). Other laboratory findings: erythrocytes  $4.43 \times 10^{12}/L$ , haemoglobin 154 g/L, haematocrit 0.479, MCV 108.2 fL, leukocytes  $19.6 \times 10^9/L$ , segmented neutrophils 53%, lymphocytes 38%, eosinophils 1%, monocytes 8% and platelets  $335 \times 10^9/L$ . Hips ultrasound: bilateral tip Ia, without visible ossification nuclei. The newborn was given vitamin K 1 mg i.m., BCG and hepatitis B vaccine. Both the mother and the newborn were released from hospital four days after the delivery.

An examination at the age of two weeks showed a vital newborn in generally good condition, with normal spontaneous motor movement, eupnoic, eucardic. It was developed according to age, well fed, with adequate weight gain (4000 g, 51 cm, head circumference 36.5 cm) and with a general impression of a healthy newborn. Asymmetric neonatal crying was still present. Neurological status was in accordance with the age and the remaining somatic status was unchanged.

Aiming to explain etiopathogenesis of the asymmetric neonatal crying and associated minor malformations and for the purpose of making differential diagnosis, we tried to confirm or exclude: microdeletion syndrome, TORCH infection or delivery trauma.

Chest X-ray showed a normally configured heart silhouette, normal vascular structures, regular pulmonary perfusion, normal transparency of lungs and mediastinum figure narrower than expected for a child at that age. Electrocardiography showed heart rate 250/min, right electric axis S to V5 and dominance of right ventricle. Since asymmetric neonatal crying is often associated with conotruncal cardiac anomalies, at the age of two weeks we performed a cardiological examination. Ultrasound of the heart showed open foramen ovale. According to the etiopathogenetical mechanism, this abnormality belongs to the abnormalities caused by disturbed intracardial flow which, according to the Clark's congenital heart defects classification, belongs to the sixth clas-

sification group. According to the positive family anamnesis (mother's brother at the age of two months was treated for left facial nerve paresis, nowadays asymmetry not noticeable; father's grandmother has partial bilateral syndactyly of the second and third toe) and a suspicion of microdeletion 22q11.2 syndrome, we performed molecular cytogenetic analysis. Conventional cytogenetic analysis of the chromosomes from the peripheral blood leukocytes showed normal female karyotype (46, XX). Molecular cytogenetic analysis using FISH probe for 22q11.2 region (commercially available LSI TUPLE1 probe) showed a normal hybridisation pattern on both homolog chromosomes 22 (46,XX.ish22q11.2(D22S75x2)).

Aiming to exclude an infection as a cause of asymmetric crying facies, TORCH serology was performed at the age of two months. Results showed congenital cytomegalovirus infection (IgM ELISA highly positive, IgG ELISA positive 1.7 IU/mL, PCR CMV plasma negative, PCR CMV urine 48000/mL, CMV specific T-lymphocytes not detected by flow cytometry). Brain ultrasound showed hyperechogenic region in thalamus and parenchyma and possible brain calcification. Magnetic resonance imaging (MR) of a central nervous system (CNS) did not verify brain calcification, or any other CNS pathology. Although otoacoustic emission during first few days of the newborn



Fig. 5. Facial symmetry while at rest at the age of five months.



Fig. 6. Facial asymmetry while crying at the age of five months.

life was normal, evoked potentials of the brain stem and tympanometry were performed and gave normal results. After receiving antiviral therapy for six weeks (ganciclovir; 2 cycles for 3 weeks), laboratory parameters decreased (IgM ELISA 1.0 IU/mL, IgG ELISA 1.9 IU/mL, PCR CMV plasma negative, PCR CMV urine 1000/mL), asymmetric crying face still remained (Figures 5 and 6), while the other somatic and neurological development of the child was normal. Control heart ultrasound at the age of three months showed spontaneous closing of foramen ovale.

## Discussion

Interest for ACF has been increased over the past few years because it is linked to congenital anomalies, especially congenital heart anomalies. Recognising congenital hypoplasia of depressor anguli oris muscle (DAOM) is also important in differential diagnosis to infectious causes of facial paresis.

Frequency of congenital anomalies among newborn with hypoplasia DAOM is 20%, compared to 2.7% in a control group. Congenital heart anomalies among DAOM newborns are evident in 6.8%, comparing to 0.45% in a control group, so it is necessary to exclude other possible anomalies, especially cardiovascular<sup>9</sup>.

Diagnosis is being established according to distinct clinical findings which include asymmetrically lowered lower lip, while temporal and nasolabial crease and eye closing on both sides remain symmetrical and intact. Ultrasound examination of facial muscles and electromyographic tests can be useful for differential diagnosis and therapy of newborn with ACF<sup>10</sup>.

Electromyography studies of facial expression support the idea that facial asymmetry is the result of asymmetry in facial muscle structure and muscle activity<sup>11</sup>.

Studies have showed that unilateral DAOM is one of a clinical signs associated with microdeletion in chromosomal region 22q11.2. It is recommended that diagnostic procedure for detecting 22q11.2 microdeletion should be performed on every child as well as on their parents<sup>12,13</sup>.

Microdeletion in a chromosomal region 22q11.2 causes variable phenotypes, including DiGeorge syndrome and velocardiofacial syndrome. About 90% of patients with 22q11.2 microdeletion have a common ~3 Mb deletion, whereas 7% of the patients have a smaller, nested ~1.5 Mb recurrent deletion. Both the ~3 Mb and the ~1.5 Mb deletions were found to occur as a result of nonallelic homologous recombination (NAHR), utilizing low-copy repeat (LCR) sequences located in the 22q11.2 region as recombination substrates. This mechanism of rearrangement explains not only the clustered breakpoints and existence of a common recurrent rearrangement among patients with chromosome 22q11.2 deletion, but also the high prevalence of de novo deletions<sup>6</sup>.

Cayler is among the first who has described 14 cases of DAOM associated with the heart abnormalities<sup>14</sup>. Nair et al. refer to embryonic defect which affects different



newborn organ systems: depressor anguli oris muscle weakness in connection to congenital heart disease in the type of truncus arteriosus and polydactily of both feet<sup>15</sup>. Akcakus et al. described newborn with ACF, tetralogy Fallot, hypopharathroidism and deletion 22q11<sup>16</sup>, Prapat et al. newborn with CULLP and diaphragmal hernia<sup>17</sup>.

Study conducted on a cohort of newborns in Israel discovered that 0.38% of them have ACF, more often on a left side (77%). In a cohort of a newborn with ACF, 7% of them had major abnormality, 3½ more often than among the total population. They are more frequent among deliveries conducted using vacuum extraction and in female newborns, but less frequent in low weight newborns. They were not more frequent among the primipar, macrosomic, premature and postmature newborns<sup>18</sup>.

Children with craniofacial malformations often have heart malformations, generally called conotruncal anomalies. Conotruncal anomalies, according to the pathogenetic developmental mechanism, belong to migration anomalies of the ectomesenchymal tissue from neural cliff and aortic arches, the second group of heart defects, according to the Edward B. Clark classification<sup>19</sup>.

Despite a better understanding of clinical signs and molecular genetics of microdeletion 22q11.2, many questions still remain to be answered. Approximately 15% of people with the DGS/VCFS/CAFS phenotype do not have typical 22q11.2 deletions. These people may have atypical deletions of 22q11.2, not recognized by currently available probes or may have point mutations within the

gene, possibly UFD1L. Paying more attention to this syndrome, especially for adult patients, should provide optimal medical care (cardiological, immunological, endocrinological) and assure cognitive functions in order to decrease invalidity of persons with a microdeletion 22q11.2<sup>20</sup>.

Some authors associate asymmetric newborn crying and TORCH infection<sup>21</sup>. Primary cytomegalovirus infection during pregnancy has a frequency of 1–4%, but in some 30–40% of cases virus spread is transplacental. Around 10% of infected newborns have manifested disease at birth, while 90% remain asymptomatic. In 0.5–1% of cases infection is the result of a maternal recurrent infection and only 1% of the newborns have symptoms at the delivery. 90% of symptomatic and 10% of asymptomatic newborns with infection develop consequences like hearing- and vision-impairment, psychomotor retardation, convulsions and microcephalia<sup>22</sup>.

According to the above mentioned examinations and diagnostic procedures, we can exclude birth injury or CMV infection as the cause of asymmetric neonatal crying. Although we did not confirm microdeletion in 22q11.2 chromosomal region, genetic etiology still cannot be excluded, especially because of the positive family history (uncle treated for paresis of the left facial nerve, grandmother with bilateral toe syndactyly). This child (or family) may have atypical deletion of 22q11.2, not recognized by currently available probes or may have point mutations within the gene or genes responsible for described phenotype.

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K. Koši-Šantić

General Hospital Virovitica, Department of Paediatrics, Gajeva 21, 33000 Virovitica, Croatia  
e-mail: [kornelija.kosi-santic@vt.t-com.hr](mailto:kornelija.kosi-santic@vt.t-com.hr)

## **ASIMETRIČNI PLAČ NOVOROĐENČADI: MIKRODELECIJA, INFEKCIJA ILI PORODNA TRAUMA? – PRIKAZ SLUČAJA**

### **S A Ž E T A K**

Asimetrični plač novorođenčadi je rijetka minor kongenitalna anomalija čiji je uzrok jednostrana ageneza ili hipoplazija mišića depressor anguli oris i depressor labii inferioris, često izolirani nalaz ili povezana s drugim kongenitalnim anomalijama, posebno kardiovaskularnim. Mikrodelecije locirane na kromosomu 22q11.2 uzrokom su nekoliko malformacijskih sindroma koje se u pojedinih bolesnika češće međusobno kombiniraju. Današnji standardni dijagnostički postupci za otkrivanje aberacija unutar kromosomske regije 22q11.2 su fluorescentna in situ hibridizacija (FISH) te metoda višestrukog umnažanja vezanih sonda (MLPA). U radu je prikazano donošeno eutrofično žensko novorođenče u kojega nalazimo u mirovanju simetrično položena oba usna kuta dok u plaču lijevi usni kut i lijeva polovica donje usnice zaostaju, parcijalnu sindaktiliju drugog i trećeg prsta oba stopala, otvoreni foramen ovale i ultrazvučno prikazane hiperehogene areale u talamusu i parenhimu mozga. Zbog upadljivog fenotipa, s ciljem diferencijalno-dijagnostičkog razjašnjenja etiopatogeneze asimetričnog plača novorođenčeta, odnosno udruženih minor malformacija, dijagnostičkom obradom nastojali smo dokazati, odnosno isključiti, mikrodelecijski sindrom, TORCH infekciju, odnosno porodnu traumu. Važnost prepoznavanja ove pareze odmah po porodu je u otkrivanju drugih povezanih anomalija, posebno kardiovaskularnih.

