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CASE REPORT

KANET Diagnosis of Fetal Akinesia Deformation Sequence at 30 Weeks

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ABSTRACT

We are reporting the case of a 40 years old 2nd gravida, 1 para. At 26 weeks of the reported pregnancy, fetal movements stopped suddenly and almost completely within 24 hours. At 30w2d she was referred for Doppler scan and fetal biometry. In ultrasonography (US) normal morphology was seen. Biometry corresponded to 28w1d. Outstanding observation was the permanent immobility of the entire fetus in four-dimensional ultrasound (4D-US). We found during two US examinations an abnormal KANET test, the first at 30w2d with a score of 3 points, and the second at 31w4d, with a score of 4 points. Cardiotocography (CTG) demonstrated complete loss of variability and accelerations. The patient developed severe polyhydramnios at 33 weeks. After lower segment cesarean section (LSCS) because of breech position, the newborn required ventilation, and passed away after 5 days.

Keywords: Fetal brain death syndrome, KANET, Fixed fetal heart rate, Fetal akinesia, Pena-Shokeir, Arthrogryposis.

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CASE REPORT

We are reporting the case of a 40 years old 2nd gravida, 1 para, with spontaneous pregnancy. This lady had an uneventful previous medical and obstetrical history of an uncomplicated first pregnancy, with normal vaginal delivery at term. In this pregnancy she had normal pregnancy surveys with normal ultrasound (US) scans at 6 and 8 weeks. She had a low risk evaluation of her 1st trimester nuchal translucency screening, and a normal morphology scan at 20 weeks. Though she changed her obstetrician thrice until 26 weeks, she adhered to regular checkups with her obstetricians every 4 weeks. She felt fetal movements first at 18 weeks and emphasized that they were more frequent and vigorous than in her first pregnancy where she started to notice fetal movements only at 21 weeks. At 26 weeks of the reported pregnancy, fetal movements stopped suddenly and almost completely within 24 hours. She went to an emergency unit where she was reassured. At 30w2d she was referred for Doppler scan and fetal biometry. In US normal morphology was detected. Biometry corresponded to 28w1d. Abdominal circumference minus 2.4 SD, cerebellum diameter minus 2.2 SD indicated moderate intrauterine growth restriction (IUGR). Apparently normal neurosonoanatomy with normal ventricular width was noticed. Normal Doppler flow parameters of fetal (umbilical artery, middle cerebral artery) and maternal side (uterine arteries) and moderate polyhydramnios were observed. Outstanding observation was the permanent immobility of the entire fetus in 4D-US. The fetus was in breech position with extended legs, the tongue was protruding from a slightly gaping mouth with moderate retrognathia, and the fists were clenched. We found during our two US examinations an abnormal KANET test, the first at 30w2d with a score of 3 points, and the second at 31w4d, with a score of 4 points. Cardiotocography (CTG) demonstrated complete loss of variability and accelerations, in repeated CTG samples with registration over more than 30 minutes each. We discussed the abnormal findings with the parents and suggested amniocentesis for karyotyping which was carried out at 30w3d. The cytogenetic report confirmed 46,XX without numerical and structural chromosomal anomalies. Parvovirus-PCR in amniotic fluid was negative. Acetylcholinesterases and alpha-fetoprotein levels in amniotic fluid were normal. At 32 weeks, our patient decided to travel to the USA for delivery. There, she developed at 33 weeks severe polyhydramnios with breathing difficulties, back pain and sleep disorder. At 34 weeks, 3.5 liters of amniotic fluid were drained per amniocentesis. The procedure was followed by onset of labor. The preterm female baby was born at 34w2d through low transverse C-section because of breech position. The baby was delivered without cries or respiration and successfully intubated on third attempt at 17 minutes post delivery and continued on positive pressure ventilation. The clinical manifestations of severe contractures, the Pena-Shokeir phenotype and the akinesia indicated the possibility of neurologic disturbance, as described below in the neuropathology report. The possibility of an intrauterine insult was considered more likely than a genetic syndrome. Postnatal brain MRI showed global volume loss of hemispheres and cerebellum, EEG diffuse low voltage and slow activity consistent with severe encephalopathy, and US demonstrated findings of bilateral intraventricular hemorrhage and increased echogenicity of bilateral basal ganglia.

After extensive discussion of the catastrophic brain damage with the parents, the baby was compassionately

extubated on day 5 post partum and passed away 30 minutes after extubation. The parents requested an autopsy.

Fetal Autopsy Report

Fetus

Dysmorphic facial features, deformed clubbed right hand, clenched left hand with severe contractures, deformed feet with severe contractures, asymmetric kidneys, no pulmonary hypoplasia.

The neuropathologic microscopic diagnosis confirmed a neonatal infant brain and spinal cord with periventricular leukomalacia, white matter gliosis, and thalamic and pontine neuronal ferrugination and gliosis. The final cause of death was considered to be generalized hypoxia as a result of a fetal thrombotic vasculopathy, placental thrombi, and placental infarcts and prematurity.

Placenta

Small, hypermature, with increased syncytial knots, fetal multifocal thrombotic vasculopathy, multiple central infarcts, intervillous thrombi.

For evaluation of possible maternal causes, the mother's coagulopathy profile was examined, and she was found heterozygous for c665C-T variant. However, only individuals who are homozygous for this variant, have elevated levels of homocysteine, with increased risk of atherosclerosis, vascular disease and venous thrombosis (Figs 1 to 5).

DISCUSSION

Fetal akinesia/hypokinesia deformation sequence (FADS) related terms:

- Arthrogryposis multiplex congenita
- Lethal congenital contracture syndrome (LCCS)
- Pena-Shokeir syndrome type I (P-SSI)
- Fetal brain death syndrome (FBDS).

Arthrogryposis is defined as a condition of congenital contractures in one or more joints. The term is not used as a specific diagnosis, but as a description of clinical symptoms, which may be found in more than 300 syndromes, and many other entities with unspecific defects. Teratogenic agents have been discussed in causing arthrogryposis, such as hyperthermia, hypoxia, ischemia, acidosis, infection, muscle relaxantia, prostaglandins, penicillamine, ergotamine,

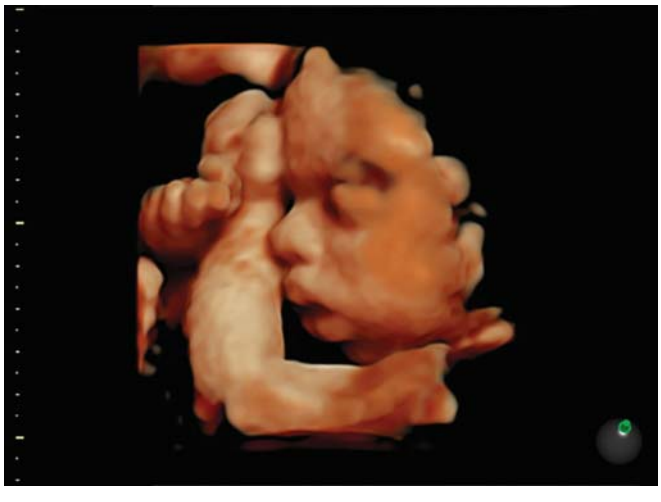


Fig. 1: Note bilateral clenched fists

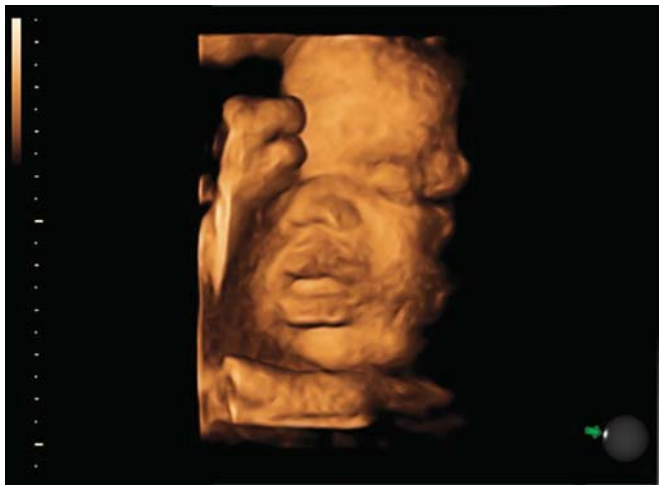


Fig. 2: Note open mouth, and slight protrusion of tongue

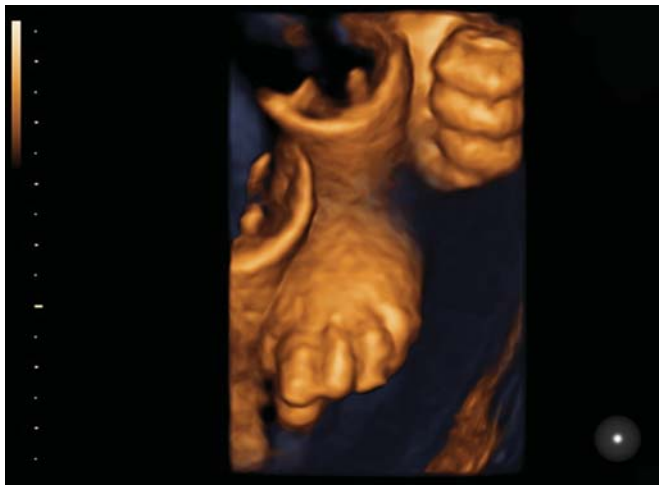


Fig. 3: Note clenched fist with adducted thumb and fixed position of first digit of the foot

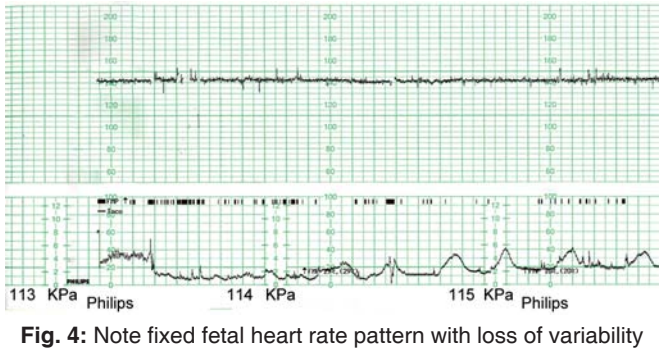


Fig. 4: Note fixed fetal heart rate pattern with loss of variability

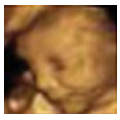
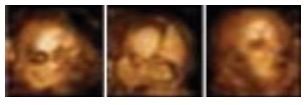
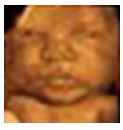
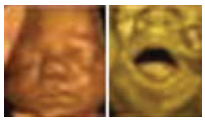
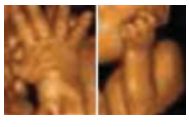
Sign	Score			Sign score
	0	1	2	
Isolated head anteflexion 	Abrupt	Small range (0-3 times of movements)	Variable in full range, many alteration (>3 times of movements)	
Cranial sutures and head circumference 	Overlapping of cranial sutures	Normal cranial sutures with measurement of HC below or above the normal limit (–2 SD) according to GA	Normal cranial sutures with normal measurement of HC according to GA	
Isolated eye blinking 	Not present	Not fluent (1-5 times of blinking)	Fluency (>5 times of blinking)	
Facial alteration (grimace or tongue expulsion)  or mouth opening (yawning or mouthing) 	Not present	Not fluent (1-5 times of alteration)	Fluency (>5 times of alteration)	
Isolated leg movement 	Cramped	Poor repertoire or small in range (0-5 times of movement)	Variable in full range, many alternation (>5 times of movement)	
Isolated hand movement  or hand to face movements 	Cramped or abrupt	Poor repertoire or small in range (0-5 times of movement)	Variable in full range, many alternation (>5 times of movements)	
Fingers movements 	Unilateral or bilateral clenched fist, (neurological thumb)	Cramped invariable finger movements	Smooth and complex, variable finger movements	
Gestalt perception of GMs	Definitely abnormal	Borderline	Normal	
			Total score	

Fig. 5: KANET uses a system of 8 fetal structural and behavioral parameters to evaluate the status of fetal neurodevelopment

enzyme inhibitors. Prenatal invasive genetic testing like chorion villus sampling (CVS) and early amniocentesis have also been linked to arthrogryposis.[1]

Pena-Shokeir syndrome (OMIM 208150) was first reported in 1974 by Pena and Shokeir as an uncommon disease characterized by congenital multiple arthrogryposis, characteristic facies often with retrognathia, intrauterine growth retardation, polyhydramnios, camptodactyly, pulmonary hypoplasia, short umbilical cord and lethality. These manifestations are usually severe, and death occurs at birth or shortly after. However, survival until 9 years, with normal intelligence, has been described.[2] 'Pena-Shokeir' is not a diagnosis or a specific syndrome but rather a description of a phenotype produced by fetal akinesia or decreased *in utero* movements. This phenotype is present in a very heterogeneous group with a variety of anomalies and etiologies. It has therefore been recommended to use the term 'fetal akinesia/hypokinesia sequence'. This term limits itself to description of both the underlying pathology and the phenotypical 'outcome,' without denomination of causes.[3] The etiology for the early cases was attributed to neuromuscular disease, with deformations and dysmorphism as consequence of weakness or paralysis of the related motor unit. In some cases, an abnormality of spinal cord motor neurons has been postulated. Recent observations have shown P-SS resulting from blockage of the neuromuscular junction, in women who express antibodies against the fetal acetylcholine receptor. The P-SS phenotype may also be caused by CNS dysfunction after intrauterine brain insults or brain malformation.[4]

Neuronal loss and ferrugination in the opercula, basal ganglia, thalamus and brainstem may be linked to the developmental form of the Foix-Chavany-Marie syndrome, or facio-pharyngo-glosso-masticatory diplegia, characterized by deficits in swallowing and facial movements, and is possibly caused by an intrauterine hypoxic-ischemic injury to the developing central nervous system (CNS).[5]

According to others, absence of fetal movements, caused by fetal neuropathy, leads to ankylosis of multiple joints, to absence of fetal breathing, in association with pulmonary hypoplasia depending on the insult timing, and to absence of swallowing causing polyhydramnios, as well as to absence of movements of facial muscles causing craniofacial anomalies.[6]

Lethal congenital contracture syndrome (LCCS) as well as Pena-Shokeir syndrome have been discussed to have an autosomal recessive gene in up to 50%.[7-9]

Performing genome scans, the LCCS locus could be assigned to a defined region of chromosome 9q34 in 5 affected individuals.[10]

Other genes have been identified to be responsible for various forms of Pena-Shokeir syndrome: DOC 7 located in 4q16.2, and RAPSN located in 11q11. Only one center analyses the disease on DNA level for scientific purposes.[11]

In one epidemiological Finnish study between 1987 and 2002, all cases with multiple contractures were collected including live born infants, stillbirths and terminated pregnancies. Of all 214 cases, 92 suffered intrauterine fetal demise [68 selective pregnancy terminations (TOP), and 24 stillbirths], 58 died in infancy. In 141 cases, the diagnosis was lethal arthrogryposis, with a prevalence of 1 in 6,985 (1.43/10,000 births). Of these, 59 had spinal cord pathology at autopsy and thus were of neurogenic origin. A total of 39 cases were diagnosed as LCCS, clinically characterized by total immobility of the fetus at all US examinations (12 weeks or later), multiple joint contractures in both upper and lower limbs, and fetal death before 32 weeks of pregnancy.[12]

Prenatal ultrasonographic diagnosis of Pena-Shokeir I syndrome with postnatal confirmation was previously described by Piotrowski and others in 2010. Cardio-tocographic abnormalities however, as in our case with a total absence of beat-to-beat variability in repeated CTG sessions, have not been mentioned.[13]

FBDS is a rare cause of a fixed fetal heart rate pattern and fetal immobility. Not many cases have been previously reported in the literature, only few of them were diagnosed prenatally. All newborns died soon after delivery.[14-16] To our best knowledge, the presented case is the first antenatal diagnosis by applying the new KANET scoring system for antenatal neurological evaluation of the fetus.[17]

FBDS is characterized by CTG demonstrating fixed fetal heart rate (FHR) pattern. A detailed Doppler- and US examination of the fetus may show initially normal neurosonographic findings as in our case, however progressive development of cerebral changes with ventriculomegaly may ensue. The clinical picture of FBDS includes polyhydramnios, total absence of fetal neuromuscular parameters of biophysical profile (BPP), and eventually the cessation of cerebral blood flow.

Neuropathology findings have demonstrated diffuse anoxic changes with multicystic encephalomalacia in both hemispheres and the brainstem, including periventricular leukomalacia, white matter gliosis, thalamic and pontine neuronal ferrugination and gliosis.

To appreciate the appearance pattern of neuro-pathological findings, it is important to remember that intrauterine brain maturation processes happen much faster than the postnatal brain development. This explains why the same hypoxic-ischemic event will generate a different

neuropathologic pattern depending on the time of the incident: the same insult will result in a white matter injury at 27 gestational weeks and in a gray matter injury at 39 gestational weeks. In the fetal and neonatal period, white matter injury is more common than injury of the gray matter. This differentiation can be used for 'dating' of the insult.[18]

Pathophysiology of abnormal fetal behavior is better understood when we remember that until delivery, subunits of the brainstem remain the main regulators of all fetal behavioral patterns.[19]

The brainstem consists of the medulla oblongata, pons and midbrain. It forms and matures in a caudal to rostral direction. Phylogenetically older structures, such as the medulla oblongata, will form and mature earlier in the gestation than pons and midbrain. In addition to its many subnuclei, the medulla gives rise to a variety of descending spinal motor tracts which reflexively trigger limb and body movements. It also hosts the five cranial nerves (VIII-XII) which exert tremendous influences on gross body movements, heart rate, respiration, swallowing and head turning. Therefore, the pathophysiology of brainstem injuries ranges from cessation of gross body movements, suspended fetal breathing, to fixed heart rate pattern and impaired swallowing causing polyhydramnios.

Methodology of Prenatal Assessment of Fetal Neurobehavior by KANET Scoring System

Abnormal fetal neurobehavior can be scored by KANET. Including the existing knowledge of structural criteria indicating neurological dysfunction, such as head circumference (HC) and overlapping cranial sutures (microcephaly), KANET uses a system of 8 fetal structural and behavioral parameters to evaluate the status of fetal neurodevelopment. The score for abnormal fetuses is 0 to 5, borderline score is from 6 to 9, and normal score is 10 and above. The first part of the assessment consists of 2D-US for the evaluation of fetal position, growth and anatomy followed by Doppler US of fetal circulation. Elevated umbilical artery Doppler pulsatility index (UA PI) > 2 standard deviations above mean for GA and reduced middle cerebral artery pulsatility (MCA PI) index < 2 standard deviations below the mean for GA, obtained in absence of the fetal movements are considered abnormal. The UA PI is measured in a free-floating loop of the umbilical cord. Measurements of the MCA PI are performed with color Doppler visualization of the circle of Willis in the fetal brain. Doppler studies are followed by the assessment of fetal behavior applying KANET test using 4D-US. The examinations were performed by an experienced operator using the GE Voluson E8 with RAB 4 3D/4D probe. The duration of examinations was between 15 and 20 minutes per fetus. All parameters of the KANET scoring system were evaluated quantitatively and qualitatively, assigning to each parameter scores from 0 to 2. Scores from all parameters were summarized forming total KANET score.[17]

While during the last 2 decades obstetricians have become a risk group in regards to medicolegal complications, there have been substantial advances in understanding the etiology of post partum diagnosed neurological impairment of the newborn.

Etiology of intrauterine brain damage is still unclear and probably multifactorial. Several pathomechanisms have been identified to play a causative role. Prenatal infection and cytokine activity are important factors in the destruction of the oligodendroglia, resulting in periventricular leukomalacia (PVL).[20] Furthermore, elevated umbilical cord plasma concentration of interleukin-6 was an independent significant predictor of developing PVL. Recent studies suggest the role of chorioamnionitis as a risk factor for cystic PVL and development of cerebral palsy (CP) in term and near term infants.[21] Considering the mechanisms of brain injury, it is still unclear, if infections/cytokines cause the damage, or if cytokines only mediate the damage. Cytokines are able to mediate intravascular cell adhesion, coagulation, thrombosis and vasoconstriction. Perinatal intracranial hemorrhage and stroke are well known risks for the development of brain damage and CP.[22] Factors contributing to the increased risk for stroke include chorioamnionitis, coagulation disorders and placental vascular pathology. The placenta is suspected to be a source for embolic material causing perinatal stroke.[23] But in 50% of all cases of fetal stroke no risk factors could be identified. Inherited and acquired thrombophilic disorders have been connected with fetal brain damage.[24]

There is a strong association between perinatal stroke and thrombophilia factors. Factor V abnormalities are associated with porencephaly and hemiplegic CP. Against commonly propagated beliefs, isolated intrapartum hypoxia was present in only 4% of severe and moderate neonatal encephalopathy. The causes of neonatal encephalopathy are heterogeneous and their etiopathogenesis may have origins in the preconception or antepartum period.[25] There is increasing evidence that, rather than being the result of intrapartum or postnatal events, many severe neurological disorders are caused *in utero*.[26] Even neurological disorders, such as minimal cerebral dysfunction, schizophrenia, epilepsy or autism, have been found to be at least partly result of prenatal neurodevelopmental impairment.[27] Also CP appears to be caused more often by prenatal than perinatal and postnatal events. Clinical and epidemiological studies have revealed that CP in 70 to 90% of cases results from prenatal rather than intrapartum causes. CP is usually caused by unrecognized, unfavorable events in midpregnancy.[28]

CONCLUSION

The new field of fetal neurology with the latest diagnostic tool KANET offers a great professional challenge. With 4D sonography, it is now possible to define reproducible parameters for the assessment of normal and abnormal neurobehavioral development *in utero*. In the presented case, with normal karyotype, normal fetal Doppler and only mild-IUGR, with (still) normal neurosonoanatomy, it was repeated abnormal KANET to reveal the true extent of fetal compromise, initiate further diagnostic measures, and appropriate counseling and mental preparation of the parents for an unfavorable pregnancy outcome.

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