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REVIEW ARTICLE

Is Kurjak Antenatal Neurodevelopmental Test Ready for Routine Clinical Application? Bucharest Consensus Statement

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ABSTRACT

Background: While two-dimensional ultrasound (2D US) is used only for the assessment of fetal startles and general movements, introduction of Kurjak antenatal neurodevelopmental test (KANET) by four-dimensional ultrasound (4D US) enabled assessment of not only movements but also some signs used in postnatal neurological assessment like cranial sutures, head circumference and finger movements of the hand for the detection of neurological thumb (adducted thumb in the clenched feast). Overall impression on general movement called by Prechtl 'Gestalt perception' is also a part of KANET assessment. These parameters cannot be assessed by 2D US, and according to our opinion they are making the difference enabling more accurate and functionally more reliable assessment of the young and immature CNS.

After Osaka standardization of KANET has been published, many studies on fetal behavior from different centers using this method have been conducted and published. Although there is lack of long-term follow-up of children who were assessed by KANET as fetuses, some conclusions on the usage of KANET test in clinical practice can be made. There are still inconclusive results of prenatal neurological assessment using KANET test in fetuses with borderline scores, although it was revealed that negative predictive value of the test as well as inter-observer reliability were satisfactory and acceptable.

Conclusion: It can be concluded that KANET test can be used in everyday clinical practice for the follow-up of fetuses at neurological risk with the strong recommendation for strict and reliable multidisciplinary postnatal follow-up till the corrected age of at least 3 years and longer whenever appropriate. This will enable to make better correlation of prenatal KANET scores with postnatal neurodevelopmental outcomes.

Keywords: Cerebral palsy, Fetal behavior, Four-dimensional ultrasound, Kurjak antenatal neurodevelopmental test, Statement.

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INTRODUCTION

After Osaka standardization of Kurjak antenatal neurodevelopmental test (KANET) has been published,[1] many studies on fetal behavior from different centers using this method have been conducted and published.[2-26] Although there is lack of long-term follow-up of children who were assessed by KANET as fetuses, some conclusions on the usage of KANET test in clinical practice can be made. There are still inconclusive results of prenatal neurological assessment using KANET test in fetuses with borderline scores, although it was revealed that negative predictive value of the test as well as inter-observer reliability were satisfactory and acceptable. It can be concluded that KANET test can be used in everyday clinical practice for the follow-up of fetuses at neurological risk with the strong recommendation for strict and reliable multidisciplinary postnatal follow-up till the corrected age of at least 3 years and longer whenever appropriate.[27] This will enable to make better correlation of prenatal KANET scores with postnatal neurodevelopmental outcomes.

Assessment of Fetal behavior by Two- (2D) and Four-dimensional (4D) Ultrasound

It is obvious that ultrasound (either 2D or 4D) can be used in the assessment of fetal behavior and that fetal behavioral patterns are reflecting the degree of development

and maturation of central nervous system.[28] Fetal movements were analyzed by 2D ultrasound and it has been revealed that assessment of fetal behavior in the specific periods of intrauterine life could make it possible to make distinction between normal and abnormal brain developmental patterns.[28] It was detected by 2D ultrasound that onset of intrauterine embryonic and fetal active movements is much earlier than subjective feeling of them by the mother.[28] When comparing assessment of fetal behavior by 2D and 4D US, than advantage of 4D is better depiction of fetal facial expressions in three-dimensions (3D) with the possibility to assess them in almost real time with the new sophisticated ultrasound machines having fast frame rates.[1-27] While 2D US is used only for the assessment of fetal startles and general movements,[28] introduction of KANET test enabled assessment of not only movements but also some signs used in postnatal neurological assessment like cranial sutures, head circumference and finger movements of the hand for the detection of neurological thumb (adducted thumb in the clenched feast).[1-27] Overall impression on general movement called by Prechtl 'Gestalt perception' is also a part of KANET assessment.[29] These parameters can not be assessed by 2D US, and according to our opinion they are making the difference enabling more accurate and functionally more reliable assessment of the young and immature CNS.[1-27]

Learning Curve, Applicability and Predictive Values of KANET

According to yet unpublished data by Panos Antsaklis, it is needed to perform 80 KANET tests by experienced ultrasound specialist in order to assess fetus by 4D US in 20 minutes. He calculated that one need 10 to 15 cases in 7 days in order to learn the basics of the technique which can be reproducible. The number of tests is comparable with other ultrasound tests like nuchal translucency screening (40 tests by experienced ultrasound specialist)[30] and anomaly scan (100–200 tests by experienced specialist).[31] In the same study on the 1712 KANET tests performed on 655 patients, the success rate for the entire test ranged between 91 and 95%. Success rate for the assessment of particular signs of the KANET was between 88% for isolated eye blinking and 100% for mouth opening and isolated leg movement. Kurjak antenatal neurodevelopmental test had almost 100% of the negative predictive value. Interobserver agreement between two examiners for different components of the KANET test were assessed by calculation of Kappa values which were lowest for the facial expression (K = 0.68) and highest for the finger movements (K = 0.84).[32] These unpublished data presented at the conference in Bucharest as oral presentation suggested that KANET test is a reliable method to be used with confidence in everyday clinical practice after appropriate education of experienced examiner.[33]

The Possibility to Detect Postnatal Neurodevelopmental Disability by Assessment of Fetal Behavior

Prechtl stated that assessment of general movements is a better predictor of postnatal neurological disability in neonates than clinical neurological examination alone.[29] This means that postnatal neurological examination done by neonatologist is not sensitive and predictive enough for the future neurodevelopmental outcome. There is a report informing that among 7 years old with cerebral palsy (CP) 47% had normal neurological examination as neonates.[34] This discouraging fact prompted researchers to investigate this phenomenon from many aspects, and our group believed that introduction of KANET could be of some significance and help to solve at least part of this problem. But the problem with prenatal and postnatal neurodevelopment is that it is taking place in different environments: prenatal with microgravity and postnatal with so called tyranny of gravity.[22] Sometimes intrauterine environment can be experienced by the fetus as hostile and unfriendly, and delivery at that moment could be foreseen as deliberation and even life-saving event.[22] Even if at that moment of assessment, KANET and postnatal neurological examination are borderline or even abnormal, it is not easy to make the prediction for the future neurodevelopment of that individual fetus and infant. This conclusion has been made on the grounds of the postnatal definition of CP as the most severe and long lasting non-progressive neurological disorder in childhood.[35-37]

Is there a Problem with the Postnatal Diagnosis of Cerebral Palsy?

The discussions on the diagnosis and definition of CP are on the debate for many years.[35-37] Based on many cohort studies and registries some conclusions have been made and diagnostic criteria have been changed.[27,35-37] Cerebral palsy has substantial lifelong effects on daily function, societal participation and quality of life for children and their families.[27,35-37] Cerebral palsy registries have provided us with some understanding of the etiologies of CP and specific outcome studies.[27,35-37] A recent systematic review investigating the rates of co-occurring impairments, diseases and functional limitations in CP, concluded that for children diagnosed at 5 years of age: 3 in 4 were in pain; 1 in 2 had an intellectual disability; 1 in 3 could not walk; 1 in 3 had hip displacement; 1 in 4 could not talk; 1 in 4 had epilepsy; 1 in 4 had a behavior disorder; 1 in 4 had bladder control problems; 1 in 5 had a sleep

disorder; 1 in 5 dribbled; 1 in 10 were blind; 1 in 15 were tube fed; and 1 in 25 were deaf.[36] With a representative cohort of children with CP from eight European countries, children are classified according to brain injury diagnosed using magnetic resonance imaging (MRI).[37] This group used a classification system based on the presumed timing and nature of the insult that resulted in CP and included both genetic and nongenetic etiologies, such as genetic cortical malformations and hypoxic ischemic injury.[37] It is necessary to attempt to determine the underlying etiology/pathogenesis to confirm the suspicion of a static lesion, exclude a treatable disorder and diagnose a malformation, which may have significant genetic counseling implications for the family.[38]

One very important environmental factor influencing development of CP is inflammation, however, no overall association has been found between antibiotic prescribing in pregnancy and CP and/or epilepsy in childhood.[38] However, an increased risk of CP or epilepsy associated with macrolide prescribing in pregnancy has been found, added to evidence that macrolide use in pregnancy was associated with serious harm.[38] Pathogenic events impacting on the brain cause different patterns of structural abnormality in CP.[38] These pathogenic events may be environmental or genetic. Their consequences will depend not only on the nature of the event, but also the timing of the event during the different stages of brain development.[38] The 1st and 2nd trimesters of pregnancy are the most critical times for cortical development and are characterized by the sequential yet overlapping steps of proliferation, migration and organization of neuronal cells and their connections.[38] Brain pathology secondary to events during these stages of brain development is usually characterized by significant malformations.[38] During the 3rd trimester, growth and differentiation events are predominant and persist into postnatal life.[38]

The limitation of many cohort studies of children with CP in Canada, the USA, and across Europe is the difficulty obtaining a representative sample and an entire cohort, while in Australia has been announced that there is the opportunity for undertaking entire prospective cohort based studies.[27] There is limited data on motor trajectories of an entire cohort of children with CP from diagnosis at 18 to 36 months of age and these motor trajectories have not been correlated with MRI brain injury classification. For the present study, the age of 18 to 24 months for entry has been chosen as diagnosis is usually confirmed by this time.[27] Children will be followed up till 5 years of age at school entry when motor outcome has been well classified.[27] The preferred age for structural MRI is from 24 months because by this age myelination of the brain should be completed, thus allowing optimum differentiation between gray and white matter on MRI, important for the detection and correct classification of brain injuries and malformations.[27,35]

In conclusion, the problem of appropriate and timely diagnosis of CP is still the issue, although many diagnostic attempts have been made and some progress has been achieved.

Is there a Possibility to improve the Outcome in Children with Neurodevelopmental Disorder by Introduction of Early Intervention?

In order to improve the outcome of neonates with high neurological risk there are very few interventions available in everyday clinical practice. Application of KANET–prenatal neurodevelopmental test, may possibly increase the ability of clinicians to define neurorisk early enough to intervene postnatally by introduction of physiotherapy. It has been speculated for many years that early application of physiotherapy can be of some significance and that it can improve neurodevelopmental outcome.[39] In Cochrane meta-analysis, it has been stated that early intervention programs for preterm infants have a positive influence on cognitive and motor outcomes during infancy, with the cognitive benefits persisting into pre-school age.[39] There is a great deal of heterogeneity between studies due to the variety of early developmental intervention programs trialed and gestational ages of the preterm infants included, which limits the comparisons of intervention programs.[39] Further research is needed to determine which early developmental interventions are the most effective at improving cognitive and motor outcomes and on the longer-term effects of these programs.[39] In one of the programs the primary caregivers have been educated about evidence-based interventions for improving infant self-regulation, postural stability, coordination and strength, parent mental health, and the parent infant relationship.[40] A therapy team consisting of a physiotherapist and psychologist delivered the 9 sessions of the program (each session was 1.5–2 hours long) in the family home over the infant's 1st year of life. Infants and their caregivers has selective long-term benefits, with caregivers experiencing fewer anxiety symptoms and lower odds of an anxiety disorder and preschoolers showing fewer internalizing behavior problems.[40,41]

Criteria for Clinical Application of Screening Tests

World Health Organization defined screening as 'the presumptive identification of unrecognized disease or defect by the application of tests, examinations, or other procedures which can be applied rapidly'.[42] Screening

tests sort out apparently well persons who probably have a disease from those who probably do not. A screening test is not intended to be diagnostic.[42] Persons with positive or suspicious findings must be referred to their physicians for diagnosis and necessary treatment.[42] In general, this definition has been taken to imply a relatively simple (though not necessarily unsophisticated) method of case-finding.[42] It is questionable whether KANET is a test for screening the disease or condition. It has been developed in order to discriminate fetuses who are at neurological risk and those who are not. Those who are at neurological risk, could have many conditions and they do not necessarily need the treatment. As it was stated in the WHO document, while screening tests may well be used in population surveys, the principal aim of surveys is not to bring patients to treatment but to elucidate the prevalence, incidence and natural history of the variable or variables under study, though case-finding is a natural by-product of surveys.[38] It is sometimes useful to use a term that refers to all forms of early detection whether by screening, physical examination or other means; and this is meant when the term 'early disease detection' has been used.[42] If we look at the WHO original criteria for screening the disease, and apply them to the KANET (Table 1), probably most of them are applicable to the KANET assessment and detection of disturbed intrauterine neurodevelopment.[42]

Table 1: How WHO criteria for screening apply to the KANET test[42]

Criteria for screening the disease	*How do they apply to the KANET test and detection of disturbed neurodevelopment*
1. The condition sought should be an important health problem.	Yes/no
2. There should be an accepted treatment for patients with recognized disease.	Yes/no
3. Facilities for diagnosis and treatment should be available.	Yes
4. There should be a recognizable latent or early symptomatic stage.	Yes
5. There should be a suitable test or examination.	Yes
6. The test should be acceptable to the population.	Yes/no
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.	Yes/no
8. There should be an agreed policy on whom to treat as patients.	Yes
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.	Yes/no
10. Case-finding should be a continuing process and not a 'once and for all' project.	Yes

Answer to the five of the 10 questions is positive and on the other five it is inconclusive (neither positive nor negative), which means that more investigation is needed in order to use KANET test as a screening tool.

Before announcing KANET test as a screening tool we have to ask ourselves the same questions as authors of before mentioned paper did almost 50 years before, like.[42]

1. What changes should be regarded as pathological and what should be considered physiological variations?
2. Are early pathological changes progressive?
3. Is there an effective treatment that can be shown either to halt or to reverse the early pathological changes?

Answer to the first question is positive, while to the second question the answer is not unequivocal, because some of the fetuses with abnormal KANET score can have normal neurodevelopmental outcome, which means that the changes found by the KANET are not progressive—quite opposite. That means that the previous answer to the first question in terms of ultimate outcome was not correct. Therefore, one who is using KANET should be aware of such possibility. The answer to the third question is positive which means that by early intervention one can halt the pathological changes, but they probably can not be reversed. If KANET is considered as the screening test for detection of neurodevelopmental disability in fetal life, than it could be probably used as selective and multiple or multiphasic screening tool.[42]

CONCLUSION

At the end, it could be concluded that KANET is ready for use in everyday clinical practice after almost 10 years of its application as the investigational tool in many studies for normal and high risk fetuses. It has acceptable sensitivity and specificity, positive and negative predictive value and inter- and intra-observer reliability. There is still one huge limitation to use KANET on clinical basis which is cost of the equipment and need for education of the medical professionals how to perform it practically. Good news is that equipment costs could be decreased quickly, but it is not in the interest of the producers to spread out the method of 4D US by lower costs of sophisticated equipment. Bad news is that not many medical practitioners are educated to use the sophisticated 4D US equipment only for medical indications, avoiding its commercial use. We hope that in the near future KANET could become a good screening tool for the selective screening of the fetuses with moderate and high neurological risk. It is still not easy to answer the question how application of KANET will affect the diagnosis and incidence of the huge group of heterogeneous,

non-progressive neurological disorders defined as CP. More studies are needed to answer this complicated and challenging question.

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