

4D Ultrasound - Medical Devices for Recent Advances on the Etiology of Cerebral Palsy

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Review

SUMMARY

Children cerebral palsy (CCP) encompasses a group of nonprogressive and noninfectious conditions, which cause light, moderate, and severe deviations in neurological development. Diagnosis of CCP is set mostly by the age of 3 years. The fact that a large number of cerebral damage occurs prenatally and the fact that early intervention in cases of neurological damage is successful, prompted

some researchers to explore the possibility of detecting neurologically damaged fetus in the uterus. This research was made possible thanks to the development of two-dimensional ultrasound technology in a real time, which enabled the display of the mobility of the fetus. Advancement of the ultrasound technology has enabled the development of 4D ultrasound where a spontaneous fetal movement can be observed almost in a real time. Estimate of the number and

quality of spontaneous fetal movements and stitches on the head, the neurology thumb and a high palate were included in the prenatal neurological screening of the fetus. This raises the question, as to does the fetal behavior reflect, (which was revealed in 2D or 4D ultrasound), fetal neurological development in a manner that will allow the detection of the brain damage.

Key words: cerebral palsy, 4D ultrasound.

1. CURRENT STATE OF KNOWLEDGE

Children cerebral palsy (CCP) encompasses a group of non progressive and noninfectious conditions, which cause light, moderate, and severe deviations in neurological development (1, 2). Cerebral refers to brain damage, while palsy related to motor disorders. Areas of brain damage is not localized with certainty, it is considered that the abnormal connections between the cortex and other brain regions. Palmer and colleagues in their study assumed that the majority of brain damage (70-90%) occurs during pregnancy, 50-10% of damage occurs during delivery, and after the delivery occurs approximately ten percent of them (1). According to research by Himmelmann et al. 38% of the causes of CCP children born occurs prenatally, during delivery 35%, while 27% are unknown causes of CCP (2). Unlike the children the same authors state that children born before the term in 17% of which CCP occurs before birth, 49% during and after child-

birth, while 33% are unclassified. It is not possible to set the CCP diagnosis prenatally (3, 4). It is usually set under the age of three years, and is defined as a group non progressive, variable motor syndromes, which occurred as a result of brain damage at all stages of its development. Together with autism and mental retardation, CCP is one of the most common causes of neurodevelopmental disorders in children (3, 4, 5, 6, 7, 8).

2. DEFINITION OF CCP

Throughout history, the definition and classification of CCP have changed. According to the latest definition, in 2006 the CCP is a group of permanent disorders of development and motor positions that lead to restriction of physical activity, resulting in nonprogressive damage of fetal or infant brain development (9). Motility disorders in children with CCP are often associated with disturbances of sensation, perception, cognitive function, communication and behavior, also epilepsy and subsequent secondary osseous

changes in muscle (9, 10). CCP was first described by English orthopedic surgeon William Little in 1860t who used the term that we could translate as “brain palsy” (9). Little is assumed that birth asphyxia is a major cause of this disorder (9). This English orthopedist’s in 1862 was the first to report that the cause is spastic for of premature birth, prolonged labor, breech births, abnormal crying and breathing, neonatal convulsions, especially in the first hours and days of life (9, 10). Little interpreted this by anoxia due to interruption of blood flow through the placenta during long-term delivery, he also thought that cerebral hemorrhage occurs due to immaturity of the neonatal brain. He described the three clinical forms of CCP in 47 children: rigidity, which affects one side of the body – hemiplegia, rigidity, which is more pronounced at lower than the upper extremities – paraplegia, and generalized rigidity (9, 10).

Sigmund Freud, neurologist, disagreed with Little’s hypothesis that the events during labor are the ma-

major cause of CCP, and he even in 1897 has determined that the disease is caused by complications during pregnancy and before birth due to adverse events during fetal development (9, 10). The term diplegia is used similarly to Little disorders involving both upper and lower extremities, in contrast to the hemiplegia, which includes upper and lower limbs on one side of the body. This term is used to describe the following disorders: rigid paraplegia, congenital generalized athetosis and corea. The causes of CCP are classified into three groups: the maternal and congenital anomalies of unknown factors, the perinatal and postnatal factors (9, 10).

Up to the present day in the literature are appearing different definitions and classifications of children's cerebral palsy. Most often cited is the definition of CCP by Bax from 1964 which reads: "CCP is a disorder of the position and mobility resulting from damage to undeveloped the brain" (10). As already mentioned today are commonly used definition of CCP was created in 2006 (9, 10).

3. THE CLINICAL PICTURE OF CCP

The clinical picture of CCP is fully expressed when the maturing process of reaching the level of topographic and functional organization and maturity, so that the final diagnosis in the majority of children can be placed only at the age of about three years or later (3, 4). During growth and development of the child we can see the motor and other neurodevelopmental disorders such as sensorineural damage, and damage to the mental, cognitive and emotional development and speech development (3, 4, 5, 6). Sometimes CCP is accompanied by mental retardation and epilepsy, which are many times more frequent in patients with CCP than in the healthy population (4, 5).

Due to the disorder of muscle tension there are the following clinical forms of CCP (4, 5, 6, 7):

- Spastic CCP, which occurs in 92% of patients;
- Choreoathetotic CCP occurs in

4%;

- Diskinetic CCP which occurs in 3%, and
- Unclassified forms of CCP which is found in 1% of patients.

Given the involvement of limbs usually are stated the following frequency of disturbance (7, 8):

- 40% of patients have hemiplegia ($\frac{3}{4}$ of children born in term);
- 30% with tetraplegia (for $\frac{3}{4}$ the cause is of fetal pathology);
- 24% diplegia ($\frac{1}{2}$ of children born at term, $\frac{1}{2}$ before term);
- 2% monoplegia (more affecting upper limbs).

Lately more and more common is diskinetic form of CCP in eutrophic children born in term, which is difficult to explain, and which suggests that the time and cause of CCP are still unclear (2). Although the frequency of CCP is relatively stable when viewed over a long period of time, it is more common in some decades than in others, and noted is its occurrence as epidemic waves (2).

In most patients with CCP we can find a correlation between clinical symptoms and disorders detected by neuroradiologic imaging methods (11, 12). European research on prevalence and etiology of CCP is based on the findings of computed tomography and/or magnetic resonance imaging of the brain in 180 children with CCP (12). In this study it was found in 13% of children with CCP a malformation of the brain, in 44% of damage to the white brain matter, in 16% the cortical-subcortical damage, in 15% the damage to the basal ganglia, while 12% of patients had normal findings (12, 13, 14). In 75% of the patients brain damage was not associated with congenital problems in brain development, and in 12% of patients despite a clear clinical picture CCP available neuroradiologic imaging methods was not possible to prove the brain damage (1, 13, 14). In the American study covering 377 children of which 273 (69%) neurological imaging methods proved the existence of a neuroradiology substrate, while in 31% was found normal neuroradiologic findings of the brain (11). Among patients with

neuroradiologic changes, in 22% of them was found the arterial cerebral infarction, in 12% of damage to the white brain matter, in 14% of congenital defects in brain development, in 7% of brain atrophy, in 5% intracerebral hemorrhage, and 2% delayed myelination (11, 15, 16, 17).

4. EPIDEMIOLOGY OF CCP

The risk of CCP in infants born in term in the United States (USA) increased in the period since 1975 to 1991 from 1.7 to 4 per 1000 live births, which means that annually in the USA, is registered 8000 new cases of CCP (11). The frequency of CCP depends on the development of the country and of its health care system and other factors, so that in developed countries is lower (ranging up to 2 per 1000 live births) in developing countries is several times higher (11, 12). Gestational age and birth weight influence the frequency of CCP so that the frequency of CCP is inversely proportional to gestational age and birth weight (3, 4, 11, 12). In Croatia there are no accurate national data on the prevalence of CCP, but according to some studies the incidence was slightly higher than in developed countries, and is 3-5 cases per 1000 live births (4).

Sweden has the best data on the frequency of CCP monitored for more than a century (18, 19). Therefore, we cite the data by the group of Swedish researchers who in their research indicated the frequency of CCP of 1.92 per 1000 live births (18, 19). This frequency did not change for the past several decades, despite advances in obstetric and neonatal care, which allowed increasing the survival rate of all preterm children, particularly that very low birth weight (2, 18, 19). Although due to the increased survival of premature infants expect the increase in the frequency of CCP in this group of children, these researchers noted an increase in diskinetic form of CCP, which occurs more frequently in the past, and eutrophic newborns, which is a worrying trend that is difficult to explain (2).

At the global level there is no unambiguous way of registering and

monitoring of children with child cerebral paralysis (12). At European Community level there is a multi-centric project, Surveillance of Cerebral Palsy (SCPE), which includes 14 centers in 8 countries (18, 19). The purpose of this project is the registration and monitoring of children with CCP in Europe. The longest tradition in the collection of epidemiological data has Sweden. According SCPE in Europe, the prevalence of CCP is 1.92/1000 live births, according to data of the American Academy of Neurology, the prevalence of CP in the world is 2 to 2.5/1000 live births (2, 12, 18, 19). The frequency of CCP is shown in Figure 1 (18, 19).

In the period since 1980 to 1990 in eight European centers was tracked the frequency of CCP depending on birth weight (12). Of the children who became ill from the CCP 21.1% had a birth weight less than 1500 g, 26.4% had a birth weight between 1500 and 2499 g, and 52.4% were heavier than 2500 grams. Children with birth weight below 1500 g represent 1% of the total population of infants, the frequency of CCP in this group was 25%, which means that in these children CCP is 125 times more frequent than in children born in term (12).

Figure 2 shows the incidence of all forms of severe and less severe forms of CCP in the period since 1976 to 1989 from which it follows that the incidence of all forms of CCP in a slight increase, while the incidence of severe forms of CCP through this entire period is equal (2, 12, 18, 19).

5. ETIOLOGY AND RISK FACTORS

Etiology CCP can be determined retrospectively in some children, and includes multiple etiological factors (20, 21, 22, 23).

Prenatal causes are:

- Diseases of the mother during pregnancy (hypothyroidism, diabetes, viral illness, preeclampsia, substance abuse).
- Proven congenital infections (toxoplasmosis, cytomegalovirus, rubella, Herpes simplex and others).

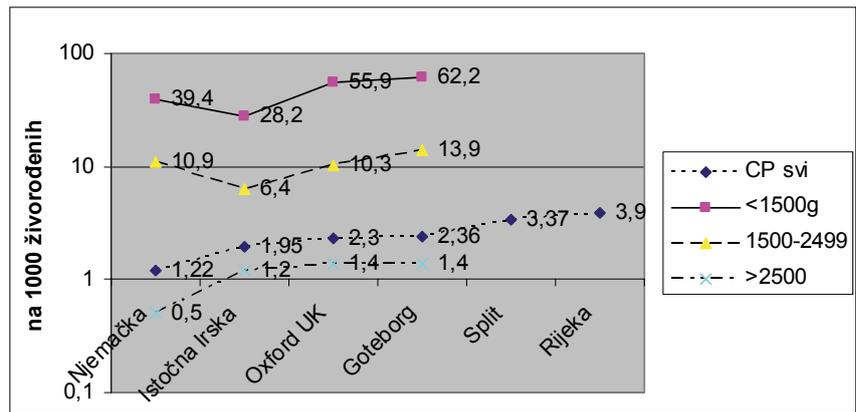


Figure 1. Prevalence of cerebral palsy depending on birth weight

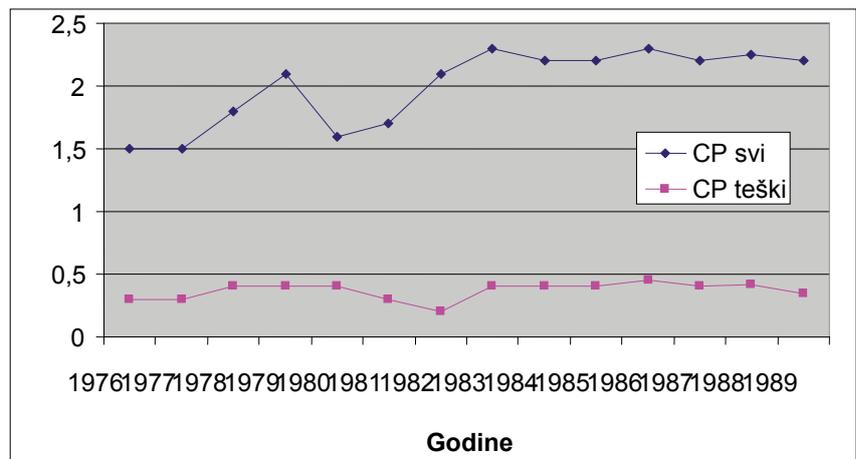


Figure 2. Prevalence of cerebral palsy in Europe in period between 1976 and 1989

- Brother-or sister with cerebral palsy.
- Genetic Disorders.
- Cerebral anomalies.
- Intrauterine brain ischemia caused by vascular obstruction.
- Blood clotting disorder of mother and fetus Rh isoimmunisation.
- Multiple pregnancy.
- Premature birth.

Intrapartal causes are:

- Intrapartal hypoxia of the brain.
- Hypoxemia (asphyxia, apnea, respiratory insufficiency).
- Intrapartalna brain ischemia (caused by asystole, bradycardia, heart failure, circulatory failure in the sepsis or other causes).
- Intracranial bleeding.
- Hypoxic ischemic encephalopathy.
- Focal periventricular leukomalacia.

Postnatal causes are:

- Sub-cortical cerebral necrosis.
- Neonatal hypoglycemia.
- Encephalitis.
- Acute metabolic crisis - (hyper-

bilirubinemia, hypoxia, hypernatremia, dehydration)-

- Standardized traumatic and non-traumatic brain hemorrhage.

Analyses show that in 40% of children with CCP whose etiology has not been established, have most probably genetic cause (24). Among the patients, a genetic cause can be determined in 48% of infants delivered in term, and 24% of premature infants. These percentages correspond to the percentage found in patients with idiopathic mental retardation (24, 25). It is believed that CCP can be caused by genetic code as much as 60% children born in term with hemiplegia, 45% children born in term with spastic diplegia, and in 32% of preterm infants with spastic diplegia in all patients with cerebral ataxia (24). Parents of children with CCP have 4.8 times greater risk of having the next child with same disorder, while the risk for twins is 29 times higher (25, 26). These facts have spurred researchers to explore the possible ge-

netic causes of CCP. Recently it was revealed six different mutations on chromosome locus 14q23.3-q24.2, which encodes a protein spastic in as a potential genetic marker (26). In some families have been found to markers located on chromosome 2q24-25 (25). For ataxic form of CCP and ataxic diplegia is responsible gene locus on chromosome 9p12q12 (26, 27).

6. DIAGNOSIS OF CCP

Diagnosis of CCP is mainly based on the clinical picture. The final diagnosis of CCP in a large number of patients can be made at the age of about three years, although in children with CCP also earlier in the period of infancy may appear different pathological signs that may indicate the development of CCP (3, 4, 24, 28). Thus, in children with CCP at age 1-3 months can be found fairly often adjustment disorder, with 6 months the coordination of movement disorders of the upper extremities, and ocular motor disorders, the presence of primitive reflexes, with 12 months more severe motor, speech disorder, and social understanding contact, with 18 months the mental retardation and impaired speech articulation and understanding (3, 4, 24, 28). Inability to walk independently at the age of 2 years testifies to the severe CCP form (21). Sometimes it happens that the neurological damage persists in 50% of children aged 7 years who are at the age of one year were neurologically impaired (3, 4). Children for whom there are deviations from the norm in the neurological status at an early age would have to be classified as high-risk group of children for the development of a neurological disorder, which does not mean that they have CCP (3, 4). Diagnosis of CCP can be set very carefully before 24 months of age, except in cases where it is extremely difficult cerebral damage (3, 4, 24, 28).

7. PUBLIC HEALTH SIGNIFICANCE OF CCP

Early detection of CCP as well as prevention and early habilitation has great public health impor-

tance. The vast majority of children with the most severe forms of CCP belong to a group of children with special needs, which requires a major organizational operations and costs (29, 30). It takes a great understanding of the community to assist in ensuring that children are enabled to live independently.

It is necessary to carry out educational and rehabilitation procedures and organization of leisure time, with education of children and their parents by organizing seminars, symposia or workshops. Organization of meetings for mutual exchange of experiences is very important for parents and their children with CCP (29, 30).

Institutional care for people with special needs in Europe in many cases is still below acceptable levels. European Social Fund is one of the instruments of the European Union to help people with special needs. Fund among others funded projects that promote independent living of these people and community services near their place of residence, including rural areas, and supports the conversion of existing facilities closed-quality service and accommodation in the community (so-called de-institutionalization) (29, 30).

8. TREATMENT OF CHILDREN WITH CCP

In the last century CCP are generally treated with orthopedic surgical procedures. Orthopedic surgeon Winthrop Phelps intensely devoted to children with CCP during forties of the 20th century introduced many new methods of treatment of children with CCP, which were based on a better understanding of the problems of sensory and motor control in these patients to avoid secondary damage caused by orthopedic treatment (29,30). Later, the treatment with physical therapy procedures aimed at reducing the effects of damage to the musculature (29, 30). Methods of treatment were very different, and their diversity testifies that opinions of the doctors about the pathophysiology of the disturbance are significantly different. So the husband

and wife Bertha and Karel Bobath in 1943 introduced neurodevelopmental treatment – NDT for children with CCP, which is still widespread and recognized, and is based on the theory of treatment in children with CCP. Bobath method of inhibiting the abnormal patterns in order to enable development of normal posture and movement (29, 30).

Vaclav Vojta, a neurologist who has worked in Czechoslovakia and Germany introduced in the eighties of the last century a new method of treatment by which in the central nervous system is trying to stimulate an innate ontogenetic motor program (29, 30). Stamer, in 2000 described that a contemporary approach to treating children with neurodevelopmental CCP has several important components (30).

The child is assessed as a single person living in a specific family with unique needs (30). The goals of treatment planning takes into account the current situation and assessment of quality of life in the future (30). The goal of treatment is to increase functional skills through a team approach to treatment and involve parents and family members in the whole process of treatment which leads to better results (30). Caregivers learn to understand the needs and the disease by reducing symptoms patient's problems. As older is a child starts problems in everyday life functioning, making it necessary to engage a wider team of experts in the treatment (physiatrists, physiotherapists, neuropediatricians, orthopedic surgeons, ophthalmologists, speech therapists, psychologists, psychiatrists, social workers, educators, lawyers, etc.) with physical therapy should begin as early as possible, because it will increase the chances of normal development by increasing the plasticity of the brain (29, 30).

There are other therapeutic approaches. The latest is TAMO - Tscharnuter Akademie for Movement Organization, therapeutic approach (30). TAMO is a new therapeutic approach to neurological and orthopedic disorders of movement, which is based on the theories of dynamics. In exchange for

learning and memory of each individual movement can learn the general rules of coordination. The therapist uses knowledge of normal development to understand the many and various ways of developing the child's skills. The treatment involved the therapeutic team, and includes family members and professional staff to spot as more damage as possible, functional limitations in children with CCP (30).

With physical therapy, occupational therapy is applied, and speech therapy, hearing, vision and orthopedic surgery. In some patients the medications are used to relax muscles and anticonvulsants. Some 20 years ago in order to relax the muscles alcohol or phenol intramuscularly were applied. After applying the alcohol effect lasted for about 4-6 months, while the effect of phenol lasted 6-8 months. Modern medicine which the main indication is the reduction of spasms is botulinus toxin that is used to weaken the muscle spasticity (30).

Disorders of fetal behavior—possible indicators of high risk factors for neurological damage.

As already mentioned CCP can not be diagnosed prenatally. CCP diagnosis is very difficult to set during infancy, and in the majority of children it is finally diagnosed until the age of 3 years (3, 4). According to current research, the majority of cerebral damage in children with CCP occurs prenatally, spurring research of prenatal neurodevelopmental detection of damage (2, 13, 14, 15, 16, 17). These surveys are developed through a two-dimensional ultrasound (2D US) technology in real-time display that allowed observing the behavior of fetus (31, 32, 33). In the last 20 years was published a large number of papers on the importance of fetal behavior in normal and high risk pregnancies (31, 32, 33).

The emergence of various fetal movements is associated with the maturation of the central nervous system (32, 32, 33). Prechtl and Visser point out that the qualitative analysis of fetal movements may provide insight into prenatal integrity of the nerve system of the fetus



Figure 3. 4D sonography showing some of the KANET parameters: facial movements, head ante flexion, mouth opening, hand to face movement, normal thumb position and finger movements, tongue expulsion.

and that this analysis could be used in the prediction of various cerebral and neuromuscular defects (31, 32, 33). Probably using a four-dimensional (4D) with it is easier to distinguish the behavior of neurologically healthy and fetus with disorder, which is especially true for facial expressions (31, 32, 33). In studies with 4D are determined the normal behavioral patterns of fetus at different gestational ages (31, 32, 33, 34, 35, 36). The resulting are standards of particular movements in all trimesters of the pregnancy based on a group of 100 normal pregnancies (36, 37, 38, 39). Besides the number of movements (quantity) their quality is also important, which includes an assessment of their diversity, fluidity and range (36, 37, 38, 39). In the fetuses with the central nervous system disorder have been found abnormal patterns of fetal behavior both in quantitative and qualitative terms (40, 41, 42, 43, 44, 45).

With the help of 4D ultrasound prenatal neurological screening test (Wolf antenatal Neurological Test—KANET), which was developed with the aim of the evaluation of fetal movement and behavior patterns, one can estimate the functional development of the central nervous system (CNS) (45, 46). The test analyzes the behavior of the fe-

tus with special emphasis on facial movements, and qualitative features of motion (Figure 3). In KANET are incorporated also the signs of brain damage from neonatal Amiel-Tisson neurological tests, overlapping sutures of the skull and neurological thumb (46).

Studies have shown that KANET detects abnormal behavior in neurologically severely impaired fetus (46, 47). Followed was the behavior of the fetus with acrania (47). Conclusively shown that in the 20th week of pregnancy fetus with acrania perform stereotyped, simple movements, of large amplitude and velocity. These movements suddenly emerged and suddenly stopped. Were absent variability of head movement, and there was no change in facial expression. In 32nd week the result was like a face mask and hand movements were simple and monotonous. At 36th week was a distinct lack of movement of limbs and facial expressions (47). With advancing pregnancy in healthy fetuses supraspinal structures increasingly involved in motor control, although not dominant. In this fetus is clearly observed pathological behavior in the absence of influence supraspinal structures. In a study that followed 120 fetuses from high-risk pregnancies, ten fetuses who postnatally had

abnormal neurological findings had been also prenatally according to KANET classified as clearly abnormal (46). Among these ten fetuses, four fetuses had alobar holoprosencephalia, one had severe hypertensive hydrocephalus, another had tanatophoric dysplasia, and four multiple fetal malformations (46). Furthermore, KANET has proven useful in identifying neurologically risky fetuses during a multicenter study that followed 228 fetuses from high-risk pregnancies, of which 18 had definite abnormal findings by KANET (47). Of these 18 pregnancies, five pregnancies were terminated, and 6 fetuses died in utero. Postnatally was neurologically followed seven infants, with abnormal findings also confirmed the findings in three fetuses (one fetus whose parents have a child diagnosed with cerebral palsy, a result of suffering from artrogriposis, and the other had aplasia vermis). Other 4 fetuses from the group with clearly abnormal KANET findings also postnatally are classified in the group with normal neurological findings. These were the fetuses of pregnancies complicated by preeclampsia, trombophilia and oligohydramnios, and one fetus has ventriculomegaly (47). Recently published results of research during which KANET test was applied to most fetuses until now—as many as 620 (100 fetuses in the group of normal, low-risk pregnancies and 520 fetuses in the group of high-risk pregnancies) (48).

Statistically was confirmed the ability of KANET in distinguishing fetuses with normal behavior of the fetuses with a moderate deviation from normal behavior, and fetuses with clearly abnormal behavior in the low-risk and high risk pregnancies (48). In the group of fetuses with abnormal KANET findings and preterm birth were the most important risk factors (48). A statistically significant difference in the result of KANET was found by comparing the fetuses of low-risk pregnancies with fetuses from the following groups: fetuses whose parents have a child diagnosed with cerebral palsy, hypertension during pregnancy (RR>160/100), threatened preterm

delivery, maternal fever, intrauterine fetal growth, Rh isoimmunisation, placental hemorrhage (48). So far, published results indicate promising opportunities of KANET in screening of neurologically risky fetuses (46, 47, 48, 49, 50, 51, 52).

The aim of prenatal diagnosis is the prenatal detection of neurologically impaired fetuses (44). What will be the meaning of prenatal detection of neurological impairment is not yet fully known, because some fetuses with pathologic prenatal screening tests after birth as infants still have abnormal neurological status, while others are completely normal (46). Further studies are necessary on a large number of fetuses and long-term neurological follow-up for children before recommendations to introduce the KANET in routine practice.

9. CONCLUSION

Further research should be directed at early detection of neurological damage during fetal and postnatal development. It is necessary to understand how risk factors in pregnancy affect the incidence of neurological damage and possible cerebral dysfunction, and thus the likelihood of CCP. Early detection of CCP allows early initiation of rehabilitation, which proves that can reduce the effects of the disease.

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