

Cerebral Palsy: A Lifelong Challenge Asks for Early Intervention

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Abstract: One of the oldest and probably well-known examples of cerebral palsy is the mummy of the Pharaoh Siptah about 1196–1190 B.C., and a letter from Hippocrates (460–390 B.C.). Cerebral palsy (CP) is one of the most common congenital or acquired neurological impairments in paediatric patients, and refers to a group of children with motor disability and related functional defects. The visible core of CP is characterized by abnormal coordination of movements and/or muscle tone which manifest *very early* in the development. Resulting from pre- or perinatal brain damage CP is not a progressive condition per se. However, without systematic medical and physiotherapeutic support the dystonia leads to muscle contractions and to deterioration of the handicap. Here we review the three general spastic manifestations of CP hemiplegia, diplegia and tetraplegia, describe the diagnostic procedures and delineate a time schedule for an early intervention.

Keywords: Cerebral palsy, early diagnosis, early intervention.

INTRODUCTION

One of the oldest and probably well-known examples of cerebral palsy is the mummy of the Pharaoh Siptah. He ruled for 6 years towards the end of the 19th dynasty (1196–1190 B.C), dying at the age of 20 (the average age for CP patients). This case of cerebral palsy is well documented in medical literature thanks to published photographs of the Pharaoh's marked foot deformity [1, 2]. In ancient Greece, Hippocrates (Greek: Hippokrates) was known as the Father of Medicine. In his work "Of the Eight-Month Foetus", Hippocrates (460–390 B.C.) discusses the association of prematurity, congenital infection and prenatal stress in relation to the pathogenesis of brain damage. He refers to children with "intrauterine disease" as having increased morbidity and mortality. He was the first to mention that "women who gave birth to lame, blind or children with any other deficit, had foetal distress during the 8th month of pregnancy" and also that "pregnant women who have fever or lost too much weight, without any obvious cause, gave birth to their child with difficulty and dangerously, or they would abort dangerously" [3-6] (see Table 1).

Concrete examples and definitions of cerebral palsy, however, did not emerge until the early 19th century with observations by William John Little; thus, Little was the first personality to intensely engage in cerebral palsy [7, 8]. Towards the end of the 19th century, two further personalities

emerged, adding to the historical hallmarks of cerebral palsy: William Osler and Sigmund Freud [9, 10]. The significant developments that have followed since then are all due to the contributions of these three personalities in the field of cerebral palsy.

Cerebral palsy is one of the most common congenital or acquired neurological impairments in children (CP, "pare-sis" (πάρεση in Greek) affecting approximately 2 to 2.5 per 1000 life births. The condition is recognised in early childhood and persists throughout life. CP is a term (*an umbrella term*) that has been applied to children predominantly suffering from motor dysfunction and related service requirements. "CP describes a group of permanent disorders of the development and posture, causing activity limitation that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication, and behaviour, by epilepsy, and by secondary musculoskeletal problems" [11].

Modern diagnostic techniques like ultrasound and magnetic resonance imaging complement the diagnostic spectrum and allow to identifying central nervous system damage reliably in early life. Any patient who is found to suffer from a certain disorder is stigmatized by the diagnosis but also gains back some of his capacity to act. Medical professionals and parents are enabled to face up to the problem, to plan therapy and to develop future perspectives for the infant. This general consideration and the need to minimize secondary changes developing in long standing CP call for an early diagnosis and treatment [12].

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Table 1. Chronological history and terminology of cerebral palsy.

Period	Name	Comments
1196-1190 B.C	Egyptian monuments and mummies	Pharaoh Siptah with deformity probably due to congenital abnormality rather than to poliomyelitis
5 th -4 th Century B.C	Hippocrates, Ploutarchos	Role of prematurity, congenital infections and prenatal stress
10 B.C.- 54 A.C Suetonius (70 A.D-130 A.D.)	Caesar Tiberius Claudius Nero Germanicus (10 B.C.- 54 A.C.)	May have also suffered from athetoid CP described "The Twelve Caesars"
1812-1820 1820-1830 1830-1831	Reil, Cazauviehl, Lejumeau, de Kergaradec Andrey, Heine, Depeck Billard, Cruveilhier, Breschet, Lallemand, Rokitansky	Reported "cerebral atrophy" in adult Reported cerebral atrophy in children
1842-1861	Hench, Little, Strommeyer	Noted an association between prematurity, prolonged labor, asphyxia, neonatal convulsions and the use of obstetrical forceps with later spastic diplegia in children
1889	Osler	First two introduce the term "cerebral palsy" and provided the first classification of CP
1891-1897	Freud	Included prenatal factors in pathogenesis of CP. Provided the most comprehensive classification for spastic diplegia
1885-1888	Mc Nutt, Gower	Described "birth palsies" and identified "first born" children as being at risk for CP.
1953	Apgar	Set a score describing an infant's condition at birth
1960	Bobath, Vojta	Need to correct abnormal postural reflexes, especially in very early life
1970-1980	Sonography, imaging	Use of brain CT/ MRI
1990	Botulinum Toxin,	Management of spasticity with Botulinum Toxin
2000	Functional MRI, PET,	Use of MRI, SPECT and PET
2000-2008	Gross Motor Function Classification System (GMFCS), Bimanual Fine Motor Function (BFMF), Manual Ability Classification System (MACS)	

CLINICAL EVALUATION

The abnormal motor status (*movement* and *posture*) is the visible core of the clinical picture of CP, and is characterized by abnormal coordination of movements and/or muscle tone. The motor impairments of CP manifest *very early* in the development of a child. The infants are usually between 12-18 months of age when the delay in psychomotor development is observed and may be even younger in severe cases. Activity limitations are a consequence of the motor disorders. Therefore, disorders of movement and posture that are not associated with limitations in motor activity are not considered part of the CP group [11].

The brain of the child with CP is in consistent neurodevelopmental conflict, as the impaired cerebral function

hampers the physiologic course of growth and maturation of the motor system as well as perception and cognition. Therefore, treatment should stimulate the development of the child in its entirety which also means to coach the whole family (family centred approach). However, due to the evolving character of symptoms, an early diagnosis and the differential diagnosis of CP may be difficult and in some cases impossible during the first 12 to 24 months of life.

According to Nelson and Ellenberg [13] there is only a weak prognostic significance of a formal neonatal examination referring to CP. The first symptoms are disturbances of muscle tone (either hypo- or hypertonic), persistence of primitive reflexes (e.g. *Moro*, *ATNR*), abnormal postures and movements and delayed motor milestones. However, these

symptoms are not CP-specific. They may be observed in all disturbances of brain development including pure mental retardation and autism, but also as a transient phenomenon of unknown aetiology with a benign outcome.

As further pathological signs, Prechtl and colleagues [14] proved the quality of spontaneous general movements (*GMs*) – particularly during the third month of corrected (postmenstrual) age – to be a reliable and valid tool for distinguishing *between* infants who are at significant risk of developing neurological deficits and infants who are not [14]. Central to the study were the age-specific “*fidgety movements*” – small movements of the neck, trunk and limbs in all directions and of variable acceleration [15]. They are the predominant motor pattern in awake infants aged 3 to 5 months [16]. Infants develop normally if such *fidgety GMs* are present and normal, even if their brain ultrasound findings indicate a disposition to neurological deficits in later life. Conversely, if *fidgety movements* are absent, infants develop neurological deficits even if their ultrasound does not indicate a significant risk [17]. However, although abnormal *GMs* are indicative for neurological deficits they are not a specific sign for CP [18, 19].

More specific symptoms are observed during the third and fourth trimesters of life when a spastic hemiplegic pattern or hypertonic patterns in the arms and legs with scissoring and increased deep tendon reflexes may develop. These signs may already indicate the type of CP. Diplegia, tetraplegia, hemiplegia and the ataxic and dyskinetic forms of CP correspond to injury in different locations of the brain, involve different cellular elements, and can be assigned to particular times of injury and different causes [12].

DIPLEGIA

In preterm infants diplegia is the typical picture of CP. Frank periventricular necrosis due to severe perinatal anoxia necessitating resuscitation (accompanied with diffuse white-matter gliosis) or diffuse white-matter-gliosis only, resulting from complications during intensive care phases (or between 25th – 33th week of the pregnancy) are the neuropathological substrates [12, 20]. The lesion is located in the border zone between long penetrators from the cortex and long basal penetrators frequently affecting the white matter anterior to the frontal horns, near the lateral corners of the lateral ventricles where the upper part of the pyramidal radiation runs. Intra- or periventricular haemorrhagic infarction damage may increase the extent of the lesion in the immature tissue of the germinal matrix [20].

There is usually a silent period of 6-12 weeks during which the above findings may subside and therefore the diagnosis may elude the clinical examination. However, a careful neurological examination in high-risk infants may reveal some suspicious neurological findings like hypotonia after the 3rd to 4th month (corrected age) of life. The child has poor head control and abnormally easily provoked primitive reflexes, especially the Moro reflex, the automatic walking and tonic neck reflexes. The examination at this stage may reveal a lethargic baby lying in a semi flexed position with

little spontaneous movement, especially of the legs [21]. *Primitive* reflexes may still persist; the asymmetric tonic neck reflex (ATNR), palmar and plantar grasp reflexes are abnormally loose. Initially hypertonia is of the rigid type with the legs extended at the knees and plantar -flexed at the ankles. Later deep tendon reflexes are hyperactive in all extremities and pyramidal signs are easily elicited.

TETRAPLEGIA

Tetraplegia commonly results from severe global hypoxic-ischemic injury which may occur at different developmental stages. Early in development this may lead to porencephaly, consisting of bilateral defects in the insula and in the gyrus praecentralis and postcentralis. Massive damaging of the immature brain tissue, such as it occurs if both Aa. carotis internae are affected, may lead to hydranencephaly. A hypoxic-ischemic injury of the brain towards the end of gestation or in early infancy may lead to multicystic encephalopathy. The alterations present as multiple bilateral cavities with varying distribution separated from each other through gliotic tissue [12].

In most cases the infant is hypotonic before the appearance of increased muscle tone. *Primitive reflexes* (Moro, automatic neck reflex) remain longer than normal; there is difficulty in feeding while later scissoring appears as well as flexion posture of the upper limbs. It is common to find hyperextension and opisthotonus in the supine position and flexion in the prone. In severe cases contractures appear as the child matures.

DYSKINESIA

Imaging Method

During the past decades new methods in brain imaging were developed providing the clinician with detailed pictures of the developmental state and possible lesions of the brain. Ultrasound (pre- and postnatal), computer tomography (CT), magnetic resonance imaging (MRI), functional MRI, transcranial magnetic Stimulation (TMS), MRI spectroscopy and positron emission tomography (PET), diffusion-tensorimaging (DTI) among others may be used during pregnancy or in the postnatal period yielding information not only about the anatomy but also on the metabolism, blood supply etc [12]. However, the possibilities to obtain data on the function of the newborn brain are still limited.

Marbled state of the basal ganglia refers to an irregular whitish appearance of the thalamus or striatum due to an abnormal network of thinly myelinated fibres running in an irregular pattern through glial scars. The anomalies are recognisable histologically at about 6 months of age and may be readily seen macroscopically when the fibres in the basal ganglia are fully myelinated. In addition to the basal ganglia the claustrum, red nucleus and subthalamic nucleus may be affected, whereas the substantia nigra, amygdala and mammillary bodies are usually spared. Marbled state may result from

prolonged delivery at term. Clinically changes in muscle tone may relate to posture and emotional state. Hypertonia is of the rigid type (*lead pipe*) in contrast to the spastic types. Corresponding to the neuroanatomical development typical extrapyramidal movements are rare during the neonatal period. They start several months later and have a slow progression. The pattern of abnormal muscle tone and movement in dyskinetic CP also progressively develops between 5 and 10 months of age and the full picture may not be completed before the age of 2 years (Foley 1992). There is a delay in the loss of primitive reflexes. Involuntary movements and abnormal posture are obvious in the second half of the 1st year of life with the clinical features completed by the 2nd year. After the 2nd year of life, the clinical presentation includes involuntary movements of athetosis, chorea and dystonia, which are more obvious in the supine position. Facial movements are affected the most [22].

HEMIPLEGIA

The typical picture of congenital hemiplegia results from a territorial infarction due to thromboembolic occlusion of an artery. The lesions are mainly seen in mature infants [23]. Complete occlusion of a cerebral artery results in unilateral focal necrosis of the brain tissue most frequently located in the territory of the left middle cerebral artery which may be explained by haemodynamic differences due to a patent ductus arteriosus and by the shorter distance between heart and left carotid artery in comparison to the right side. Occlusion of the vessel leads to hemiplegia of the trunk, arm and head. In contrast, infarction in the territory of the anterior cerebral artery results in a paresis of the leg [12]. Proximal occlusion of the middle cerebral may also involve the anterior cerebral artery resulting in a complete hemiplegia. In pre-term infants the hemiplegia often originates from periventricular haemorrhagic infarction (and periventricular leucomalacia).

ATAXIA

Ataxia may also be a feature of CP. A decreased cerebellar volume was found in severely premature newborns especially after prolonged artificial respiration [24]. Patients with ataxic CP have fewer neurological complications when compared to other types of CP. Ataxic CP presents with hypotonia during early infancy and delay of the gross motor functions. After the 6th month, the lack of balance is obvious. These children are clumsy/unskillful and unable to perform precise and quick movements. This type of CP is *characterised* by significant heterogeneity both for its aetiology and for the clinical appearance. However, diagnosis can be misled. The clinical findings can be ensured by ultrasound and other imaging and laboratory methods.

THERAPY

The decision on a therapeutical intervention is guided by several considerations [25]:

1. neural plasticity and critical periods of development,

2. extent of brain injury and signs predicting prognosis,
3. familial environment, and
4. concepts and goals of intervention.

Ad 1) Due to the plasticity of the developing nervous system it may adjust to an injury depending on the time and location of the impact. The plasticity is based on several factors:

- growing axons may take alternative routes to their targets,
- each hemisphere initially develops cortico-spinal projections to the ipsi- and contra-lateral extremity,
- a large fraction of neurons go into apoptosis between gestational week 32 and the early postnatal period suggesting that the surplus of neurons may adopt other functions if connected to proper targets [26],
- growing dendrites and remodelling dendritic fields, which are regulated by activity [27], in adult rats a sustained neocortical neurogenesis has been documented after neonatal hypoxic/ischaemic injury, which could contribute to the ability to recover from injury [28],
- Rha *et al.* [29] treated rats with unilateral cerebral injury inflicted at postnatal day 7 after a time interval of 4 weeks in different environments and found a significantly higher generation of new neurons in the sub-ventricular zone in animals that lived in an enriched environment. Kolb *et al.* [30] demonstrated that a reduced growth of dendrites of pyramidal neurons after focal cortical lesioning in newborn rats was reversible if the animals were housed comfortably and received tactile stimuli.
- In children with uni- or bilateral cerebral lesions who were examined by means of TMS between the 3rd and 24th month of life a progressive reduction of synaptic connectivity was found due to lack of cortico-spinal activity [31]. These findings were confirmed in cats. Uni-lateral inactivity of the cortico-spinal tract resulted in aberrant cortico-spinal terminations and decreased numbers of interneurons as well as M1 motor map defects. However, early electric stimulation of the injured extremities and training restored cortico-spinal tract connections and the M1 motor map [32, 33].

The animal data thus suggest critical periods for the motor development which would correspond to an age of several months up to one year in humans.

Hence, severe damage will regularly result in early and severe symptoms whereas small or focal injuries that occurred early in gestation are better adjusted for and will become clinically apparent only later.

Ad 2) Location and extent of the CNS lesion primarily defines the development of the child and the efficacy of the

therapy. Severe injuries cause deficits which are often only partially compensated for by therapy. However, this does not exclude the possibility of substantial improvement by activation of remaining functions like improvement of vision in children with neonatal damage in the occipital lobes.

Repeated investigations of the brain in the first postnatal weeks and months by ultrasound and MRI generally render the more valuable information concerning prognosis [24, 34, 35] than performing just one investigation at a fixed date [36].

Van Wezel-Meijler *et al.* [37] conducted a study on very premature or low birth weight neonates evaluating the prognostic value of repeated ultrasound investigations. The ultrasound findings were complemented by MRI at the calculated date of term. In cases where a periventricular echo density was observed in at least one investigation a white matter lesion was seen in MRI and in children with peri- or intraventricular haemorrhage (Volpe grade I-III) this was always confirmed by MRI indicating an unfavourable prognosis. Normal ultrasound findings always indicated a favourable course even if the MRI showed conspicuous findings. The study thus confirmed in part older investigations [38].

Numerous follow-up investigation of severely premature children confirm a high risk for developmental retardation in CP including global cognitive impairment or developmental disorders of scholastic skills which may only be noticed in school [39-41]. Hence the concept of a therapy only addressing motor skills seems to be outdated.

CP in mature newborns is relatively rarely caused by hypoxia-ischemia. Prognosis in these cases is deduced from the clinical course assessed according to the modified classification of Sarnat and Sarnat [42]. The brain injury usually is observed in conjunction with other pre- and perinatal complications like intracranial haemorrhage, seizures or connatal disorders. Early clinical symptoms are similar to those described above; later tetraparesis may develop which commonly is associated with cognitive and emotional retardation.

Ad 3) The significance of the family for the development of the child is increasingly acknowledged. Family centred therapeutical concepts are now available like COPCA (Coping with and caring for infants with special needs) which includes informing the parents about the child's disorder and coaching them to involve the child in a broad spectrum of activities [43]. Further, the parents themselves need support with their fears and worries [44] and should be involved in the management of the child in an emancipated way [45, 46]. 2011.

Ad 4) In the past different physiotherapeutic techniques and concepts have been developed to diminish the neurologic symptoms like extensive passive cross-pattern exercises of the extremities, similar to the movement pattern of amphibians for "neurological organisation" [47-49] or intensive passive training by inducing the coordination complexes "reflex creeping" and "reflex rolling" to create the basis ("start level") for a normal motor development [50, 51] and inhibition of abnormal movement patterns response reflexes

and facilitation of more or less normal patterns of posture and purposeful movements [52, 53]. More recently multidisciplinary treatment strategies have been recommended which do not any longer solely focus on the movement disorder. The Bobath concept has also been changed accordingly. Reflecting current neurobiological insights into the mode of function of the therapeutical measures the regimens include a family centred approach [54], and comply with many elements used in the preventive exploitation of high-risk infants. The therapists train parents and carers in ways to assist their child to achieve best performance [55]. In general, advanced motivation and inspiration of the intrinsic activity of the child is the focus of therapy so that an increased sensorimotor experiences can be gathered and functional improvement achieved. The patient becomes the active part in the setting, with increase of age pathological movements are accepted. Catchwords for therapy are: *Practice makes perfect; Use it or lose it; Fire together – wire together; No changes without reward.*

Priority is given to the accomplishment of everyday tasks, largely independent of the quality of the movement sequences as long as this does not worsen pre-existing contractions. However, although the early developmental intervention programs in preterm infants improved cognitive function at the infant age they showed no long term effect when assessed at the school age. In systematic reviews performed by Orton *et al.* [56] and Blauw-Hospers *et al.* [57] there was little evidence of an effect on motor functions in the short-, medium- or long-term. Thus in children in whom CP or a severe psychomotor retardation develops the aims of intervention have to be individually and constantly adjusted over years according to the individual (dis)abilities. The efficacy of a concept that is not solely focused on motor development has previously been shown in a controlled trial with spastic diplegic children, between 12 and 19 months of age [58].

A systematic literature analysis documented a relatively good efficacy for constraint induced therapy, hip surveillance, botulinum toxin, selective dorsal rhizotomy, context-focused therapy, goal-directed training, fitness training and purpose-built home training programmes given that the indication is individually adapted [59].

In the last decade children have been treated with hemiplegic CP intervention programs to overcome the "learned non-use" in adult hemiplegia, which are strongly child- and impairment orientated. The efficacy of the constraint-induced movement therapy (CIMT) and the hand-arm intensive bimanual therapy (HABIT) depends on the cooperation of the child which can be expected not before an age of about 4 years. The efficacy depends also on the size of the cerebral lesion and the extent of ipsi-lateral projections which can negatively influence the result [60, 61]. Although the effects of CIMT were evaluated in several therapeutic trials an optimal protocol for therapy could not be established and a long lasting improvement of quality of life for the children was not proven until now [62].

Cognitive development is much less at risk in congenital hemiplegia or after perinatal stroke than in spastic diplegia

or tetraplegia [63]. Occupational therapy and physiotherapy are indicated in motor symptoms differing between right and left side.

TIME SCHEDULE FOR AND EARLY INTERVENTION

Prevention

The risk factors for CP could be identified by a meta-analysis in children born mature. However, there is only a small chance to avoid the risk factors [64]. In cases of perinatal illnesses such as fits, respiratory distress syndromes or hypoglycemia timely state-of-the-art clinical management helps to prevent irreversible brain injury. Preventing birth before the 34th week of gestation is one of the most important concerns since these children have a risk of about 50 % to develop CP. Medical care should aim at.

- reduction of multiple births after in-vitro fertilisation,
- early recognition and treatment of prenatal intra-amniotic infections or sepsis and possible sequelae [65-67].
- in case of habitual abortion or preterm delivery examination of the fetus and the mother to identify individual causes followed by adequate pre-conceptual counselling of the mother, and
- critical analysis of the data gained by fetal electronic monitoring [68, 69].

Most of the very premature children are treated in hospital and require long term intensive care and artificial respiration. In order to prevent further complications like haemorrhagic stroke any stress should be avoided and gentle physical contact should be offered [70]. The parents need to be involved in the management of the child as early as possible. Previous studies have shown that this may shorten the stay in hospital [71, 72]. However, whether this regimen also influences psychomotor development has not been shown conclusively. According to Guzzetta *et al.* [73] massage of the baby diminishes stress and fosters development. Both, premature children and children at high risk should be seen frequently by a paediatrician after discharge from the hospital to take preventive measures as early as possible [74, 75].

Therapy

At the age of 3 months high-risk infants with a birth weight of less than 1250 g who suffered from severe pre- and/or perinatal complications (which may lead to CP) and who showed neurological abnormalities at term as well as alterations in CNS imaging should be neurologically re-evaluated and their motor development should be assessed according to criteria of Prechtl or Hadders-Algra respectively [14, 25]. Children with suspicious findings should be seen again after 4 weeks. If functional abnormalities are confirmed interventions are initiated as described above. This proceeding, which differs from former concepts, is indicated because confirmed abnormal neurological findings point to

serious deficits in psycho-motor development and a risk of

CP. The treatment has to be adjusted to any peculiarities that may appear later like disturbed motor function of the mouth, cognitive retardation etc. making use of the different forms of therapy like speech or occupational therapy and physiotherapy respectively. Later more specific interventions are indicated like HABIT, CIMT or treadmill training.

The first thing should be to inform parents and /or caregivers carefully about the possibility that the baby has a developmental retardation and that there is a risk that the child can develop a form of CP. According to Hadders-Algra [25] it is important to coach parents and inform them about all facts that could influence the developmental process. Children have to explore their ADL-surrounding and make experience, favourable seems to be an ADL-setting how and where problems have to be solved and children have to adapt in their performance.

Despite great efforts in research many open questions remain in CP [12, 14, 16]. The main goal should be to continue identifying the divergent aetiologies and to prevent CP in order to reduce the percentage of children with brain damage. Herskind *et al.* [76] argue that infants offered early intervention in future clinical studies must be identified carefully, and that the intervention should be focused on infants showing early signs of CP to determine an effect of treatment.

In *summary*, the most important points concerning in early treatment are

- to start general supportive activities within the first year of life to achieve the best possible benefit for the child,
- to assure a loving and stimulating atmosphere during the training and to perform the exercises with the family members or the next caregivers,
- to provide not only technical guidance but also psychological and psychosocial support to the caregivers,
- to communicate not only active but also passive interventions such as in feeding, bedding and head control (handling) to the caregivers in order to help to avoid contractures or hip dislocation,
- to adjust the treatment setting individually and include frequent repetitions and positive feedback to promote the essential intrinsic motivation and self-activity,
- to promote sensorimotor (and mental) development analogous to that in normal children; it may be necessary to divide the training in very small development steps,
- to implement specific and targeted therapies or even CIMT at an appropriate age. For example, training the hand-mouth movement is a goal-oriented activity which is possibly achieved only with the support of the postural control, and
- to address associated symptoms separately such as deficits in oral motor skills or eating disorders.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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