Review Article

Neonatal seizures and epilepsies

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ABSTRACT

Neonatal seizure is the most frequent clinical manifestation of central nervous system dysfunction in the newborn. It is defined as a paroxysmal alteration in neurologic function that include motor, behavior and/or autonomic functions occurring in the first 28 days after birth of a term neonate or before 44 weeks of gestational age in a preterm infant. Seizures in the presence of encephalopathy are the most important clinical pattern of an acute cerebral insult in the immature brain. Chronic epileptic disorders very rarely may have their onset in the neonatal period and may persist well into infancy and later childhood. Structural brain defects and metabolic disorders constitute a substantial proportion of this group. Ictal EEG recordings remain the gold standard for the accurate identification of neonatal seizures of cortical origin and for the distinction from non-epileptic paroxysmal events. This review focuses on the electroclinical patterns of neonatal seizures and epilepsies with an emphasis on the classification and terminologies. The current therapeutic options are also highlighted briefly.

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1. Case 1

A baby boy was delivered at term following a prolonged labor. He had significant fetal distress and the Apgar was 5 at 1 minute. He was resuscitated and transferred to the Neonatal Intensive Care Unit (NICU) for ventilator support. He continued to be lethargic with poor cry and started showing abnormal stereotyped movements on the 2nd day of life. Metabolic evaluation was noncontributory. Electroencephalogram (EEG) showed burst suppression pattern (Fig. 2). Magnetic Resonance Imaging (MRI) of the brain on the 6th day of life showed features suggestive of hypoxic ischemic encephalopathy. He was treated with phenobarbitone and the seizures got controlled over the next 72 hours. He was discharged on the 10th neonatal day. There was no recurrence of seizures and phenobarbitone was tapered and stopped after one month. On follow up at 3 months, he had not attained head control or social smile. There was mild spasticity of the limbs.

Neonatal seizures are the most frequent clinical manifestation of central nervous system dysfunction in the newborn with an approximate incidence 1.8–3.5/1000 live births. 1 Seizures with encephalopathy as described in case 1 form the

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Fig. 1 — Normal EEG of a ten day old term newborn boy in the modified neonatal montage. EEG channels are organized as initial 8 channels showing longitudinal derivations and the next 4 channels showing transverse derivations. Extra cerebral channels include electrooculograms, limb and chin EMGs, abdominal movement and EKG. (Paper speed 30 mm/s, high frequency filter 70 Hz, low frequency filter 1 Hz, Notch filter 50 Hz, 7 μV/mm).

Fig. 2 — Term newborn with severe hypoxic ischemic encephalopathy associated with neonatal seizures. EEG in the modified neonatal montage shows suppressed electrical activity with frequent generalized bursts of high amplitude sharp and slow waves (suppression — burst pattern) indicating a severe brain insult. Note that the paper speed is 15 mm/s to better appreciate the suppression — burst pattern (High frequency filter 70 Hz, Low frequency filter 0.5 Hz, Notch filter 50 Hz, 10 μV/mm).
most important clinical pattern for an acute cerebral insult in the immature brain. Peripartum asphyxia with subsequent development of hypoxic ischemic encephalopathy constitutes one of the important causes for neonatal seizures in the developing countries with a median prevalence of 38–48%.2,3

2. Definitions

According to the International League Against Epilepsy (ILAE), an epileptic seizure is best defined as an electroclinical phenomenon characterized by a transient occurrence of signs and symptoms due to an abnormal, excessive or synchronous neuronal activity in the brain.4 However, neonatal seizures are traditionally defined as paroxysmal alterations in neurological function that includes motor, behavior and/or autonomic function occurring in the first 28 days after birth of a term neonate or before 44 weeks of gestational age in a preterm infant.5 It is to be noted that this purely clinical definition, unlike the electroclinical definition of ILAE, is entirely arbitrary, resulting in both over and underestimation of the number of seizures in the newborn.6

Several studies have shown the existence of considerable inter-observer variability among physicians and allied health professionals in the clinical diagnosis of seizures in the newborn ICU.7 In view of this, ictal EEG recording may be considered as the gold standard for the accurate identification and characterization of neonatal seizures.8

Electrographically documented neonatal seizures with or without clinical manifestations might represent the most accurate concept of neonatal seizures. However, prolonged EEG monitoring on critically ill term/preterm newborn with multiple hemodynamic supports is technically very demanding. Fig. 1 shows the modified 10/20 montage, which has been found to be a sensitive and specific technique in this setting.6 Because of the technical complexity and the need for special expertise in the recording and interpretation of EEG in the neonatal ICU setting, a significant number of centers in the resource poor countries are still relying on the clinical identification of seizures. A recent WHO guideline on neonatal seizures also recommended the use of EEG for the confirmation of suspected neonatal seizures at all the levels of care.9

3. Classification

Neonatal seizures belong to a clinically heterogeneous group. A significant majority of them occur in relation to acute brain insults and may be conventionally included in the acute seizure category. They are usually self limited or may effectively be treated with specific therapy as in hypocalcemia or hypoglycemia. However, some of the chronic epileptic disorders may originate in the neonatal period and persist well into infancy and later childhood. Structural brain defects and metabolic disorders constitute a substantial proportion of this group. Even though genetic epilepsies are considered relatively benign in the neonatal period, catastrophic genetic epilepsies like KCNQ2 encephalopathy are increasingly being discovered.10

Seizures in newborn are many times very subtle and difficult to identify and characterize appropriately unlike in older children and adults. This is mainly due to the immaturity of the nervous system resulting in high incidence of electrographic seizures without any clinical correlates. Moreover, many abnormal movements in sick newborns will be misinterpreted as seizures, if simultaneous EEG monitoring is not available. Conversely, neonatal seizures may clinically mimic many motor behaviors normally exhibited by newborns, thus leading to underestimation of the seizure burden. Many unique features of neonatal seizures like asynchronous clonic movements in bilateral spread and migrating focal seizures are also attributed to the immaturity of the neural networks.

There are two most widely accepted classification schemes for neonatal seizures.3,11 The traditional classification system put forward by Volpe is purely clinical and is solely based on the semiology of the most prominent movement in the seizure.5 According to this classification, seizures in the newborn were mainly divided into 1) clonic, 2) tonic, 3) myoclonic and 4) subtle. However, this classification system needed modifications in view of the inherent limitations in the clinical identification of neonatal seizures as described in the previous sections. Later on Mizrahi and Kellaway described a classification scheme, where the clinical semiology was coupled with putative pathophysiology based on ictal electrographic features.11 According to this scheme, epileptic neonatal seizures are considered to be generated by hypersynchronous discharges of a critical mass of cortical neurons. These events cannot be initiated by tactile stimulation and cannot be suppressed by restraint of involved limb or repositioning of the infant. These are consistently associated with electrographic seizure activity on the EEG. Focal clonic, focal tonic and myoclonic seizures are commonly shown to be associated with EEG features. Behaviors characterized by tonic posturing or myoclonic like movements, especially in encephalopathic babies, may not show electrographic signatures. These events may mostly be considered as brainstem release phenomena or reflex behaviors, although sometimes they may be seizures. When non-epileptic, they may be provoked by stimulation and suppressed by restraint or repositioning. Pure electrographic seizures without any clinical manifestations comprise the third group in this classification scheme. This electroclinical classification scheme was a major step in bringing neonatal seizures closer to other groups of epileptic seizures. However, the terminology of non-epileptic seizures in this classification refers to a group of pathophysiologically heterogenous phenomena as described above and needs further refinement.

The clinical and EEG features of the major types of neonatal seizures are summarized below.

3.1. Clonic seizures

Clonic seizures may either be focal or multifocal and are sometimes difficult to differentiate from non-epileptic events like jitter. These seizures are more frequently seen in term infants than in preterm infants and are almost invariably associated with evolving trains of theta and alpha range frequencies in the EEG. Clonic seizures which involve both sides of the body simultaneously are usually asynchronous unlike true generalized clonic seizures in older individuals.
Multifocal clonic seizures may alternate between regions within a particular seizure, or may migrate from one region to another. Initially, the electrographic seizures may be of a certain frequency in one region followed by a completely different frequency in another region reflecting the immaturity of the neonatal cortical circuitry. For the same reason, classical Jacksonian march, focal seizures with secondary generalization or generalized tonic clonic seizures may not be seen in neonates. Focal clonic seizures are usually associated with focal structural lesions like cortical malformations or infarcts.

3.2. Tonic seizures

Tonic seizures may be focal or generalized. Focal tonic seizures are usually associated with EEG changes and may denote focal cortical lesions. Generalized tonic seizures are characterized by sustained bilateral extension or flexion of the limbs or trunk, resembling decerebrate or decorticate posturing. Generalized tonic seizures usually do not have electroencephalographic correlates. Ictal EEG findings are commonly seen when there are associated autonomic or focal motor phenomena. Generalized tonic seizures are generally observed in severely encephalopathic babies and may indicate poor prognosis.

3.3. Myoclonic seizures

Myoclonic seizures are seen in both preterm and term neonates. They may or may not have EEG correlates. Myoclonic movements associated with EEG changes are also called “cortical myoclonus”, while myoclonus with no EEG correlate is termed “sub-cortical myoclonus”. The seizures may be focal, usually involving muscles of one upper extremity; or they may be generalized or multifocal. Generalized myoclonus consists of bilateral symmetric jerks of the limbs or trunk. Multifocal or “fragmentary” myoclonus is characterized by brief asynchronous twitching of different muscle groups. Of the three types, fragmentary myoclonus is the type least commonly associated with EEG changes.

3.4. Motor automatisms

Motor automatisms, previously called subtle seizures may usually occur in encephalopathic neonates. These are very difficult to characterize without simultaneous EEG. Ocular movements are the most common type of automatisms seen in newborn. In preterm infants, the most common manifestation is sustained eye opening with unresponsiveness and eye fixation. In full term infants, horizontal sustained deviation of the eyes is usually seen. A variety of paroxysmal changes in autonomic activity such as alterations in breathing, heart rate, blood pressure, salivation, sweating and color changes of the skin have also been described. Epileptic automatisms such as oculomotor movements, lip smacking, bicycling movements and apnea are more frequently seen in preterm infants than in term infants. Autonomic changes of epileptic origin usually occur in association with other clinical, behavioral or motor phenomena and this may be a useful feature to differentiate them from non-epileptic events. Apnea of epileptic origin was found to be more associated with bradycardia in an earlier study. Many of these behaviors were found to be inconsistently associated with EEG changes in the scalp, raising the possibility of reflex behaviors in a severely dysfunctional brain. However, the possibility of an epileptic nature for some of these events cannot be ruled out with certainty. These seizures may be originating in the deeper limbic structures spreading downstream to brainstem or subcortical structures without propagation to the cortical surface and scalp, especially in severe encephalopathies.

3.5. Status epilepticus

Several studies have shown that neonatal seizures may last up to 1–5 min and majority of seizures stop before 3 min. Status epilepticus denotes a very high seizure burden and is traditionally defined as an unusually prolonged seizure or recurrent seizures without regaining the baseline neurological status. However, a vast majority of the neonatal seizures are associated with encephalopathy as a result of the underlying pathophysiology, rather than as a consequence of recurrent seizures. In view of this, the status epilepticus in the newborn is differentiated based on the sole criterion of the duration of seizures and is operationally defined as a prolonged continuous seizure lasting for 3 min or recurrent seizures whose total duration exceeds 50% of the given epoch or both. It has been shown to be more common in term neonates compared to preterm infants. In babies who are administered neuromuscular paralyzing agents to optimize cardio-respiratory care during mechanical ventilation, overt seizure activity may often be absent. In these cases, episodic autonomic phenomena like paroxysmal tachycardia or hypertension could suggest seizures.

4. EEG characteristics

An electrographic seizure in the newborn is usually defined as a sudden, repetitive, evolving and stereotyped episode of abnormal electrographic activity with amplitude of at least 2 μV and a minimum duration of 10 s. If the interval between two adjacent electrical events is less than 10 s, they are considered as one single event. Electrographic events meeting the criteria for seizure except for the duration are called brief rhythmic discharges (BRD) or brief intermittent rhythmic discharges (BIRD). These discharges have been shown to be associated with pathologies like neonatal hypoglycemia and periventricular leukomalacia and may be predictive of adverse developmental outcome. Electrographic seizures are common in the term newborn and are usually seen in the central and temporal regions. The seizure discharges may consist of repetitive spikes, sharp or slow waves, or a combination of different waveforms. Seizures may remain localized to a specific area, slowly spread to involve contiguous regions, abruptly involve one hemisphere, or migrate to the other hemisphere. Persistent electrographic seizures without associated clinical activity may be seen in severely encephalopathic babies and also after treatment with antiepileptic drugs.
Interictal EEG may not be useful in the diagnosis of neonatal seizures and it may show nonspecific negative sharp transients in central and temporal regions in both term and preterm neonates (Fig. 3). Positive rolandic sharp transients are mostly associated with periventricular leukomalacia and germinal matrix hemorrhage in preterm babies. However, interictal EEG may clinically be useful in encephalopathic babies with seizures and may suggest possible etiologies for the seizures, help in determining degree of cerebral dysfunction, risk for persistent seizures, and prognosis for long term outcome. Depressed undifferentiated background, suppression burst pattern (Fig. 2) and multifocal sharp transients indicate diffuse brain dysfunction, and may suggest a bad prognosis. Persistent focal interictal anomalies like focal spikes and slow waves may point towards a focal cortical lesion. However, the prognostic value of the EEG depends on the day of recording. Neonatal EEG done sufficiently early may serve as a prognostic indicator for both seizure and developmental outcome. Normal EEG suggests a good prognosis, while the presence and persistence of diffuse abnormalities on serial EEGs may suggest poor outcomes.

5. Pathophysiology

Seizures occur more frequently in the neonatal period than at any other time in life. Basic science research has identified several factors, which might contribute to the enhanced excitation in the immature brain. Developmental imbalance between the maturation of excitatory and inhibitory circuits is supposed to be the most important factor for the increased seizure burden in the newborn. Immature brain has high concentration of extracellular potassium, which may contribute to the increased excitability. The newborn brain is also vulnerable to a variety of insults like hypoxia and hypoglycemia, further increasing the chance of seizures. Recurrent and prolonged seizures produce several biochemical and metabolic changes in the brain which may have both short term and long term prognostic implications. Long term consequences of neonatal seizures also depend up on various other factors like the etiology and the age at which seizures occurred. The long term effects of exposure of antiepileptic drugs (AEDs) on the immature and developing brain are not clear. Several basic science studies suggested that neonatal exposure to some of the currently available antiepileptic drugs (AEDs) may possibly affect the developing brain. However, there is no convincing clinical data available which unequivocally prove that short term or long term antiepileptic drug therapies adversely alter cognitive function, irrespective of the etiologies.

6. Diagnosis and management

The diagnosis of neonatal seizures is based on clinical observation to a significant extent, especially in the neonatal ICU. In an encephalopathic baby, the threshold for the clinical diagnosis of seizures is very low. The proportions of both clinical seizures without electrographic correlation and electrographic seizures without obvious clinical correlates are found to be high in the acute setting. The various factors contributing to this interesting phenomenon have been described earlier.

There are many differential diagnoses for neonatal seizures in the acute setting. Slow roving eye movements and orofacial movements may be physiological and are very

Fig. 3 – Interictal EEG in the modified neonatal montage showing independent negative sharp transients over both central regions (Paper speed 30 mm/s, high frequency filter 70 Hz, low frequency filter 0.5 Hz, notch filter 50 Hz, 7 μV/mm).
difficult to differentiate from subtle seizures. Jittery or tremulous movements are usually seen in metabolic and electrolyte anomalies and drug withdrawal. They are stimulus sensitive and may be modified by positioning. Physiologic myoclonus in sleep otherwise called benign sleep myoclonus has normal EEG findings (Fig. 4). Hyperekplexia, a genetic disorder due to a mutation in glycine receptor gene, is characterized by stimulus sensitive myoclonus, muscle rigidity, episodes of tonic spasms and rarely apnea.28

A vast majority of neonatal seizures are acute symptomatic in origin. Table 1 lists the common etiologies for acute neonatal seizures. A detailed review of individual etiologies and their management is outside the scope of this review. Although determining etiology should not delay the treatment of seizures, in certain circumstances, etiology-specific therapy alone is required to control seizures. This is particularly true when seizures are secondary to metabolic disturbances such as hypoglycemia, hypocalcemia, hypomagnesemia, hyponatremia, hypernatremia, hyperammonemia or in pyridoxine dependent epilepsy.

If a newborn with acute encephalopathy shows paroxysmal motor or behavior manifestations suspected to be a seizure, the current practice is to immediately initiate antiepileptic drug (AED) administration pending etiological evaluation. It is uncertain whether the same protocol is appropriate if the baby is otherwise normal. It would be prudent to perform further evaluation and positively confirm the diagnosis before the AED administration.

Physiologic factors unique to the neonatal period should be taken into consideration before initiating AED management. Intravenous route is considered most suitable for administration of AEDs in the acute setting in view of the immaturity of gastrointestinal absorption in neonates. Phenobarbitone is traditionally preferred in the dose of 15–20 mg/kg loading dose followed by maintenance dosages of 3–5 mg/kg/day. Phenytoin and benzodiazepines have also been used with varying success. Newer antiepileptic drugs like levetiracetam and topiramate have also been used in a few clinical series.27

Recently, basic science data has suggested a possible role of some AEDs in the pathogenesis of ‘electroclinical decoupling’ of neonatal seizures.28 The clinical relevance of this finding is not clear and further studies are needed before making firm management recommendations.

Therapeutic hypothermia is emerging as a useful neuroprotective strategy for babies with neonatal seizures and hypoxic ischemic encephalopathy. In a prospective study of 69 newborns who underwent video EEG monitoring for neonatal seizures, 51 babies who received therapeutic hypothermia had a significantly less seizure burden after controlling for the severity of injury. This therapeutic effect was seen more in children with mild to moderate HIE.29

### 7. Prognosis

Neonatal seizures combined with an acute encephalopathy carry a significant risk for morbidity and mortality. Mortality was in the range of 25–30% earlier, which has come down over the years with improvement in neonatal care.14 There is a 20–30% risk for long term developmental consequences like cerebral palsy, mental retardation and epilepsy.30,31 Most important predictors of both short term and long term outcome are etiology and degree of brain injury. Diffuse disorders like hypoxic ischemic encephalopathy, intraventricular hemorrhage, infections and cerebral malformations carry a worse prognosis compared to transient disorders like hypocalcemia or focal disorders like infarcts.14 The clinical semiology of seizures and background EEG abnormalities may point towards degree of brain involvement and may have prognostic implications.32 Several studies had highlighted the

Fig. 4 – Ictal EEG of a child with benign sleep myoclonus in the modified neonatal montage. The tibial EMG activity is noted without any ictal cerebral activity. (Paper speed 30 mm/s, high frequency filter 70 Hz, low frequency filter 0.5 Hz, notch filter 50 Hz, 15 μV/mm).
utility of serial interictal EEG in predicting the long term developmental outcome.\textsuperscript{33,34} Myoclonic seizures, generalized tonic seizures or motor automatisms in the setting of encephalopathy and interictal EEG anomalies like burst suppression pattern may indicate diffuse brain involvement suggesting poor neurodevelopmental outcome. Normal EEG is found to be a good prognostic indicator in up to 80% of cases.\textsuperscript{7,24}

### 8. Neonatal epilepsies

Epilepsies as defined by the ILAE very rarely start in the neonatal period. Etiologically, neonatal epilepsies may be classified as structural malformations of cerebral cortex, metabolic diseases and genetic epilepsies. Neonatal epileptic syndromes may be further classified into benign syndromes and epileptic encephalopathies based on their neurodevelopmental and seizure outcome.

#### 8.1. Benign neonatal epilepsies

**Case 2**

A term newborn baby of nonconsanguineous parents started having very frequent seizures from third day of life. Seizure burden was very high with multiple seizures every day. She did not have any signs of encephalopathy in between the seizure episodes. MRI brain and metabolic evaluation were normal. There was a history of paroxysmal neonatal events in the father. However, there were no clinical records and so the details could not be verified. Interictal EEG showed independent negative sharp transients over both central regions. Ictal EEG showed asymmetric and asynchronous tonic clonic seizures with no consistent focus (Fig. 5a, b). She was treated with multiple antiepileptic drugs and cofactors without response. Seizures remitted completely on the 20th day of life after introduction of levetiracetam. There was no recurrence of seizures and development proceeded normally. At the time of last follow up at 12 months of age, the development was completely appropriate for the age. Sleep EEG did not show any epileptiform abnormalities. Genetic studies for potassium channel mutations were not performed.

Benign neonatal epilepsies are characterized by transient seizures and good neurodevelopmental outcome. There are two types; benign familial neonatal seizures and benign non familial neonatal seizures. Benign familial neonatal seizures otherwise called benign familial neonatal convulsions (BFNC) is an autosomal dominant potassium channelopathy affecting the KCNQ2 and KCNQ3 genes.\textsuperscript{35} The seizures start usually in the first week, 80% in the second or third day. The seizures are usually brief and occur multiple times per day in an otherwise normal baby without any precipitants. Family history of similar episodes in the newborn period is usually noted. Clinical seizures may be partial or generalized with asymmetric tonic or clonic motor activity associated sometimes with motor automatisms and apnea. Ictal EEG usually shows generalized suppression. Interictal EEG may show nonspecific abnormalities. Prognosis is generally good with resolution of seizures by six months and normal neurodevelopmental outcome. These seizures are usually treated with antiepileptic drugs in view of their frequency.

Benign non familial neonatal convulsions usually start around the 5th day of life in normal babies without any adverse antecedent history. The etiology and pathogenesis of the seizures are unknown. The following diagnostic criteria have been proposed: (i) Apgar score greater than 7 at 1 min, (ii) typical interval between birth and seizure onset (4–6 days), (iii) normal neurologic examination before seizures and interictally, (iv) normal laboratory findings (metabolic studies, neuroimaging, and CSF analysis), and (v) no family history of neonatal seizures or post neonatal epilepsy.\textsuperscript{36} The typical episode is a cluster of focal clonic movements which last for several hours and sometimes ending up as status epilepticus. Ictal EEG may show focal rhythmic spikes and slow waves sometimes spreading diffusely. Interictal EEG may show a characteristic abnormality of theta pointu alternans, which is a discontinuous, non-reactive, 4–7 Hz theta activity that frequently alternates between hemispheres and is intermixed with sharp activities occurring both in wakefulness and sleep. Seizures remit by around 48 h of onset. Most of the children are treated with AEDS in the acute setting. Long term neurodevelopmental outcome is generally good.

#### 8.2. Neonatal epileptic encephalopathies

Early Infantile Epileptic Encephalopathy (EIEE, Ohtahara syndrome) and the Early Myoclonic Epileptic Encephalopathy (EMEE, Aicardi Syndrome) are the two named epileptic encephalopathies with onset in the neonatal period.\textsuperscript{37–39} Both the syndromes are associated with resistant epilepsies and poor neurodevelopmental outcome along with suppression burst pattern in the EEG. Ohtahara syndrome is usually seen with severe structural malformations of the brain and the main seizure type is tonic spasms from the beginning. On the other hand, EMEE is usually associated with multifocal myoclonus and is mostly associated with inborn errors of metabolism. The interburst interval is longer in EIEE compared to EMEE. Sometimes, the burst suppression pattern in EIEE may not be appreciated at disease onset, and follow up EEGs may be necessary to make the diagnosis. Seizures are typically refractory to currently available anticonvulsant medications. Outcome is uniformly poor for both the syndromes with a high rate of mortality in early infancy. Surviving children may develop hypsarhythmia at around 3–6 months with classical features of west syndrome. In view of the similarity in several clinical features including age of onset, EEG features and outcome, it has been hypothesized that both EIEE and EMEE may represent a continuum of epileptic disorders.\textsuperscript{38} In addition to these named syndromes, epileptic encephalopathies associated with resistant focal seizures due to large hemispheric
dysplasias may also have the clinical onset in the neonatal period. They might need early surgical management.

9. Conclusion

Neonatal seizures are clinically heterogeneous. A vast majority of them are symptomatic as a result of acute insults to the developing brain. Identification and characterization of the seizures in the newborn may be made more objective by the use of long term EEG monitoring. Chronic epileptic disorders may very rarely have their onset in the neonatal period and some of them may have a benign outcome. The catastrophic epileptic syndromes are mainly due to structural cortical malformations or inborn errors of metabolism. Early diagnosis and appropriate management of neonatal seizures may be helpful in improving the long term neurodevelopmental outcome.

Conflicts of interest

Both the authors have none to declare.
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