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Commentary

Neonatal encephalopathy: Case definition & guidelines for data collection, analysis, and presentation of maternal immunisation safety data

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1. Preamble

1.1. Background on neonatal encephalopathy

To improve comparability of vaccine safety data, the acute neonatal encephalopathy working group has developed a case definition and guidelines neonatal encephalopathy applicable in study settings with different availability of resources, in healthcare settings that differ by availability of and access to health care, and in different geographic regions.

The definition and guidelines were developed through group consensus. They are grounded on both expert opinion and a systematic literature review related to the assessment of acute neonatal encephalopathy as an adverse event following immunisation and to the diagnosis of acute neonatal encephalopathy in humans.

Encephalopathy is a general term used to define disease, malfunction or damage of the brain. The major symptom of encephalopathy is an altered mental state [1]. Defining altered mental state in the newborn is significantly more challenging than in the adult and there are no established direct measures to determine level of consciousness in the newborn. Nevertheless, specific clinical signs reflecting neurological function correlate with the overall severity of the encephalopathy. These clinical signs have been grouped in stages, usually three of them: mild, moderate and severe as in the Sarnat classification. The Sarnat criteria remain as the most commonly accepted classification [2,3].

Neonatal encephalopathy has several potential etiologies and acute hypoxia-ischemia is the most studied cause. Over the years, the term "neonatal encephalopathy", has been used by many as a

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synonym of "Hypoxic-ischemic encephalopathy". The reason is that other etiologies are often reported as a specific diagnosis, as in the case of inborn errors of metabolism (e.g. non-ketotic hyperglycinemia), infections (e.g. meningitis) and other specific causes. It is therefore imperative to emphasize that many different processes leading to neonatal encephalopathy may develop prenatally, at birth or immediately post-delivery, and result from mainly, but not exclusively, genetic, metabolic, infectious, and traumatic processes. The common denominator in neonatal encephalopathy is the loss of homeostasis which can lead to abnormal brain function and potentially to brain structural changes [2–4].

Investigations such as magnetic resonance Imaging and neurophysiological technologies such as electroencephalography and evoked potentials are aids in exploring the severity and prognosis of neonatal encephalopathy, but are not required for its diagnosis. MRI brain can be reported normal in 15–30% of cases of confirmed mild cases (Sarnat 1) of hypoxic ischemic encephalopathy [1,5].

The EEG is the most specific test to confirm and diagnose that a clinical paroxysm is epileptic in origin [9]. Electrographic pathological patterns correlate with neonatal seizures during seizure recording and subtle or subclinical seizures can often only be diagnosed by EEG monitoring. Once anti-seizure medications are administered, up to 58% of treated neonates exhibit electroclinical uncoupling, in which the clinical signs of their seizures vanish despite the persistence of subclinical electrographic seizures [9].

EEG however has important technical limitations in the recording of some epileptic seizures, particularly those originating in mesial or midline areas of the brain. Also EEG is not always readily available for recording in the NICU. Amplitude integrated EEG (aEEG) is becoming widely used by neonatologists. This recording compresses the time scale of conventional EEG. It has lesser spatial resolution and is less sensitive for the detection of neonatal seizures compared to long term monitoring by conventional EEG [10,11]. Abnormalities on the neonatal EEG such as discontinuity of the background or central sharp waves are not specific and will vary depending on external factors such as gestational age, body temperature during therapeutic cooling and medications [7].

Therefore, as per World Health Organization guidelines on neonatal seizures, the most practical method of diagnosis is the clinical recognition of neonatal seizures [8].

The Task Force on Neonatal Encephalopathy group on Neonatal Encephalopathy and Neurological outcome published in 2014 a comprehensive document defining Neonatal encephalopathy as "a clinical syndrome in an infant born at or beyond 35 weeks of gestation, manifested by a subnormal level of consciousness or seizures, and often accompanied by difficulty with initiating and maintaining respiration and depression of tone and reflexes" [5]. It was the consensus of our group to replace the word "consciousness" with the word "alertness" since the definition of "consciousness" is more vague. We also considered it necessary to include in the definition the concept of multiple potential etiologies.

When assessing encephalopathy in a newborn younger than 35 weeks of gestation, normal neurological development may prevent specific behavioral reactions and reflexes to be tested, making semiology unreliable. Furthermore, the diagnosis of "encephalopathy of prematurity" is heavily based on neuroanatomical changes seen on MRI or autopsies rather than acute clinical signs [2,6].

Considering the limitations for diagnosing and timing encephalopathies in the preterm newborn, this review defines Neonatal encephalopathy as a clinical syndrome presenting with abnormal functioning of the central nervous system, in the earliest days of life in an newborn (up to 28 days of life) born at or beyond 35 weeks of gestation, manifested by an abnormal level of alertness or seizures, and often accompanied by difficulty with initiating and maintaining respiration and depression of tone that may be due to a variety of etiologies including hypoxia/ischemia, metabolic disturbance, or infection.

This definition is to be equally applied in vaccinated or unvaccinated populations.

1.2. Methods for the development of the case definition and guidelines for data collection, analysis, and presentation for neonatal encephalopathy as an adverse events following maternal immunisation

Following the process described on the Brighton Collaboration Website http://www.brightoncollaboration.org/internet/en/index/process.html, the Brighton Collaboration Neonatal Encephalopathy *Working Group* was formed in 2016 and included members of clinical, academic, public health and industry background. The composition of the working and reference group as well as results of the web-based survey completed by the reference group with subsequent discussions in the working group can be viewed at: http://www.brightoncollaboration.org/internet/en/index/working_groups.html.

To guide the decision-making for the case definition and guidelines, a literature search was performed using Embase.com (Medline/PubMed + Embase); ClinicalKey (eBooks); ScienceDirect (eBooks); StatRef (eBooks) and the Cochrane Library.

Several different research platforms were utilized in this search for references focused on maternal vaccination and encephalopathies. These platforms included electronic books, systematic reviews, and other journal literature. The following three search parameters which included a variety of synonyms were combined; pregnancy, vaccines, and encephalopathy.

This search resulted in several general book chapters discussing various types of neonatal encephalopathy. There were no Cochrane reviews that focused on this topic. The journal literature search produced 33 results that included subject headings or keywords for vaccines, pregnancy and encephalopathy. The results were limited to those published since 2005. The results were further limited to either reviews or major/prospective clinical studies.

1.3. Temporal versus causal association with maternal immunisation

There are no reports of encephalopathy following immunisation in the pregnant woman or the newborn. There is hence no uniformly accepted definition of Neonatal Encephalopathy following immunisations. This is a missed opportunity, as data comparability across trials or surveillance systems would facilitate data interpretation and promote the scientific understanding of the event.

1.4. Periodic review

Similar to all Brighton Collaboration case definitions and guidelines, review of the definition with its guidelines is planned on a regular basis (i.e. every three to five years) or more often if needed.

3. Case definition of neonatal encephalopathy[3]

For All Levels of Diagnostic Certainty
Newborn (1–28 days) born at or beyond 35 weeks of gestation
Level 1 of diagnostic certainty (Definite)
Abnormal level of alertness or seizures (see footnote 1)
AND
Difficulty with initiating and maintaining respiration
AND
Depression of tone

[3] For Seizure definition see Ref. [12].