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Commentary

Congenital microcephaly: Case definition & guidelines for data collection, analysis, and presentation of safety data after maternal immunisation

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1. Preamble

1.1. Need for developing case definitions and guidelines for data collection, analysis, and presentation for congenital microcephaly as an adverse event following maternal immunisation

Congenital microcephaly, also referred to as primary microcephaly due to its presence in utero or at birth, is a descriptive term

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for a structural defect in which a fetus or infant's head (cranium) circumference is smaller than expected when compared to other fetuses or infants of the same gestational age, sex and ethnic background.

Congenital microcephaly can be diagnosed either postnatally or prenatally and is usually defined by the measurement of occipital-frontal circumference (head circumference) that is more than 2 standard deviations (SDs) below the mean for age and sex or less than the 3rd percentile for age and sex [1–3]. Severe microcephaly is defined as head circumference more than 3 SDs below the mean for age and sex [4–7].

Congenital microcephaly may occur as an isolated structural birth defect or in combination with other birth defects. Physiologically, congenital microcephaly is a disorder of reduced brain size and volume resulting from abnormal fetal development. Microcephaly has been associated with intellectual disability [8].

In addition to congenital microcephaly, there is also an acquired form of microcephaly in which an infant's head circumference falls within the normal range at birth with subsequent development of microcephaly over time due to deceleration of brain growth. Classifying microcephaly as either congenital or acquired is the currently favored nomenclature rather than the past designations of "primary," "pure," or "true" for congenital microcephaly versus "secondary" or "syndromic" for acquired microcephaly. We have focused on congenital microcephaly for this case definition and will not address acquired microcephaly.

The term "relative microcephaly" is used when an infant is below standard weight and length for gestational age and sex with a proportionally small head circumference measurement. This constellation may be associated with a better intellectual prognosis than "absolute microcephaly" or congenital microcephaly, in which weight and length are normal for gestational age and sex [4]. Terms such as microcephaly or microencephalia are used interchangeably when referring to reduction in brain mass, rather than decreased head circumference. Thus, despite congenital microcephaly typically being associated with a small head circumference, in the case of hydrocephalus, since there can be reduced brain mass with a normal or enlarged head circumference due to enlarged ventricles from excess central nervous system fluid it would still be considered microcephaly.

A variety of estimates of the incidence of congenital microcephaly have been published in the literature, reflecting the heterogeneous definitions and methods used. Studies evaluating population level prevalence are limited as most available reports are based on small case numbers and focus on discrete populations such as individuals with cerebral palsy or musculoskeletal defects, making these studies poorly generalizable.

Incidence rates of congenital microcephaly have been estimated to vary between 0.58 and 1.87 per 10,000 live births in studies conducted in the United States and Europe [9]. While a series of 360 births with congenital microcephaly in Missouri, United States in the 1990s suggested a population incidence of more than 7 cases per 10,000 births [10], more recent data estimate congenital microcephaly rates from 2 to 12 cases per 10,000 livebirths [11].

There are very limited data on the prevalence of congenital microcephaly in low and middle-income countries (LMIC). A systematic review of 9 studies from India indicate a pooled prevalence rate of newborns with congenital microcephaly of 2.3 per 10,000 births (95% confidence interval [CI] 1.82–2.78) among 97,155 births [12]. An increase in the reported prevalence of microcephaly was noted in some areas of Brazil during 2015 where there was confirmed Zika virus transmission [13]. Prevalence of microcephaly in the 15 states of Brazil with laboratory-confirmed Zika virus transmission was 2.8 cases per 10,000 live births, which was significantly higher than in the four Brazilian states without Zika virus transmission (prevalence 0.6 cases per 10,000 live births). Another review from North Eastern Brazil employing three different criteria showed markedly varying rates [14]. In this review covering a period from 2012 to 2015, reported prevalence rates among 16,208 infants ranged from 2.1 to 8.0% based on the different criteria for congenital microcephaly used. It should be noted that in addition to microcephaly, Zika virus infection has been associated with other neurologic and brain abnormalities, which can be found in the absence of microcephaly [15–20].

The causes of congenital microcephaly are extensive, highly variable and heterogeneous, and include both known and undetermined aetiologies. Any condition that affects the process of brain growth can result in microcephaly [21]. Table 1 is a reproduced table which provides an extensive list of genetic disorders including metabolic disorders, perinatal brain injury due to maternal disease or teratogen exposure (including in utero drug or toxin exposure and infectious agents such as toxoplasmosis, rubella, cytomegalovirus, Herpes simplex, syphilis, parvovirus B19, and varicella [TORCH infections]) during pregnancy [22]. These in utero exposures along with postnatal brain injury due to infections,

Table 1
Causes of primary *[congenital]* microcephaly: overview.

1. **Genetic causes**

Numerical chromosomal aberrations or microdeletion and/or duplication syndromes

Trisomy 13, 18, 21, etc.

Monogenetic microcephaly

- Autosomal recessive microcephaly (MCPH1-10, MCPHA)
- Nijmegen breakage syndrome (MIM#251260)
- Autosomal dominant microcephaly
- X-chromosomal microcephaly
- Aicardi–Goutieres syndrome (MIM#225750, 610329, 610181, 610333, 612952)
- Cockayne syndrome (MIM#216400, 133540, 216411)
- Cornelia de Lange syndrome (MIM#122470, 610759, 614701, 300590, 300822)
- Rubinstein–Taybi syndrome (MIM#180849)
- Feingold syndrome (MIM#164280, 614326)
- Rett syndrome, congenital (MIM#164874)
- Mowat–Wilson syndrome (MIM#235730)
- Smith–Lemli–Opitz syndrome (MIM#270400)
- Seckel syndrome (MIM#210600, 606744, 608664, 613676, 613823, 61472)
- Ligase IV syndrome (MIM #606593)
- Mutations in ATRX gene (MIM*300032)
- Mutations in ARX gene (MIM*300382)
- Mutations in PQBP1 gene (MIM*300463)
- Mutations in ASNS gene (MIM*108370)
- Borjeson–Forssman–Lehmann syndrome (MIM#301900)

Imprinting disorders

Angelman syndrome (MIM#105830)

2. **Metabolic cause (genetic aetiology)**

Serine biosynthesis disorder
Sterol biosynthesis disorder
Mitochondriopathy, e.g. pyruvate dehydrogenase deficiency
Congenital disorders of glycosylation syndrome
Rare congenital metabolic diseases (see text)

3. **Exogenic factors**

Intrauterine infection

- Toxoplasmosis, rubella, cytomegalovirus, herpes simplex, varicella zoster virus, syphilis, human immunodeficiency virus, Zika Virus[a], Lymphocytic Choriomeningitis Virus (LCMV)[a]

Teratogens

- Alcohol, cocaine, antiepileptic drugs, lead/mercury intoxication, radiation

Disruptive incident

Vascular incident (stroke), intrauterine death of twin

Maternal disease

- Hyperphenylalaninaemia
- Maternal anorexia nervosa

Extreme insufficiency of placenta

4. **Craniosynostosis**

Reproduced with permission from Von der Hagen et al. [22].
[a] Not included in original table from Von der Hagen et al.