

Incidence, aetiology and neurodisability associated with severe microcephaly: a national surveillance study

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ABSTRACT

Objective To determine the incidence, causes and neurodevelopmental impact of severe microcephaly (head circumference <-3SD) up to age 2 years.

Design Bi-national active paediatric surveillance study undertaken 2017-2018 to identify and characterise new diagnoses of severe microcephaly.

Setting United Kingdom (UK) and Republic of Ireland (RoI).

Participants Infants aged under 12 months at diagnosis.

Interventions Observational study.

Main outcome measures Incidence, aetiology and neurodevelopmental outcomes at age two years.

Results Fifty-nine infants met the case definition, of whom 30 (51%) were girls, 24 (41%) born preterm (<37 weeks gestation), and 34 (58%) of 'White' ethnicity. Eight (14%) children died before age 12 months. Incidence of severe microcephaly was 5.5 per 100 000 infants (95% confidence intervals [CI] 4.0, 7.3). Higher relative risk (RR) was associated with preterm birth (RR 7.7 [3.8, 15.1]) and British Asian ethnicity (RR 3.6 [1.6, 7.8]). Microcephaly was mainly due to genetic causes (59%), brain ischaemia/hypoxia (10%), and congenital infection (8%), and 19% remained undetermined. Each child was referred on average to eight specialists and 75% had abnormal brain imaging. By age 2 years 55 children experienced neurodevelopmental abnormalities, including feeding problems (68%), motor delay (66%), visual impairment (37%), hearing loss (24%) and epilepsy (41%).

Conclusions Although severe microcephaly is uncommon, it is associated with high mortality, complex multimorbidity and neurodisability thus represents a significant ongoing burden for families and healthcare services. Potentially preventable causes include preterm birth, hypoxic/ischaemic brain injury and congenital infections. Clinical guidelines are essential to standardise aetiological investigation and optimise multidisciplinary management.

Keywords: paediatrics; neurodevelopmental disorders; epidemiology; aetiology; microcephaly

INTRODUCTION

Babies with microcephaly have a 'small head' due to poor head growth prenatally or in early childhood. Affected babies can exhibit a range of serious neurodevelopmental and cognitive problems, including epilepsy, vision and hearing problems, cerebral palsy, and learning disability.^{1,2} The causes of most microcephaly cases are unknown and clinical management is therefore aimed at mitigating these associated neurodevelopmental difficulties. Timely detection and investigation, confirmation of neurodisability, provision of genetic counselling and access to wider health and care services are essential to support families who have a child affected lifelong by microcephaly and representing a significant cost³ to health services. Importantly, our limited understanding of long-term outcomes⁴⁻⁶ represents a key barrier to effective delivery of care.

Severe microcephaly is defined as a head circumference more than 3 standard deviations (<-3SD) below the mean for age and sex.¹ As the UK lacks a centralised registry for birth head size, it is unclear how many babies are born with severe microcephaly each year. Contemporary estimates in the UK vary widely from 0.8 to 1.4 per 10 000 births reported by congenital anomaly registers^{7,8} to 30 per 10 000 babies in one regional birth cohort study.⁹ Enhanced surveillance in 2016 suggested the impact of congenital Zika infection on microcephaly incidence in the UK was very small¹⁰ but also highlighted concerns about the ability of existing passive congenital anomaly systems to identify increases due to novel causes.

To address uncertainty about the burden of severe microcephaly in infants and its contemporary causes, we conducted active surveillance throughout the UK and Republic of Ireland (RoI) in 2017 and 2018. In this paper, we estimate the incidence and describe the causes of new diagnoses of severe microcephaly, and report neurodevelopmental outcomes at two years of age.

METHODS

This was a prospective, bi-national, cross-sectional study with cases ascertained through active surveillance. Between 01 October 2017 and 31 October 2018, all new cases of severe microcephaly were identified by 3860 consultant paediatricians in the UK and Ireland, who report monthly to the British Paediatric Surveillance Unit (BPSU; www.rcpch.ac.uk/bpsu) surveillance system. The overall card response rate by paediatricians was 91.5% (42633 of 46618 cards) in 2017-2018.¹¹ Clinicians reported all live born infants aged up to and including 12 months of age who were newly diagnosed with severe microcephaly, defined as a head circumference $<-3SD$ for age and sex OR <0.4 th percentile ($<-2.67SD$) on the standard UK growth chart. We excluded babies with anencephaly. The cut-off of 0.4th centile is the closest centile to $-3SD$ on the growth chart that is included in the Personal Child Health Record (PCHR or 'Red Book') to routinely monitor UK newborns. Head circumference was adjusted for gestation at birth. Anonymised clinical information was provided by paediatricians from existing medical records at diagnosis and age one and two years. Children were classified into Census 2011 ethnic categories. Using the Index of Multiple Deprivation (IMD) score¹², children's residential postcodes were assigned to deprivation quintiles.

The primary cause of microcephaly was identified from the clinician report and classified by the study team using a hierarchical taxonomy (eFigure 1) which was informed by the classification described by von der Hagen⁶ and refined through consensus amongst the research group. Clinicians were asked to report if genetic testing had been undertaken, if a genetic cause had been identified and, if it had, what this was. Only children with a genetic mutation that had previously been associated with microcephaly were considered to have a 'confirmed' genetic cause, the others were assigned to 'probable' or 'possible' genetic cause depending on the likelihood of the association. Associated conditions and exposures were also recorded, including maternal exposures (alcohol/ drug use/cigarette smoking), craniosynostosis, other congenital anomalies, intrauterine growth retardation, and parental consanguinity.

The study was reviewed by East of Scotland Research Ethics Committee (reference: 17/ES/088); the Health Research Authority Confidentiality Advisory Group (reference: 17/CAG/0126); and the Public Benefit and Privacy Panel, Scotland (reference: 1718/0184).

Two patient charities, *Contact* and *sense*, supported the study and will disseminate findings. A staff member from *sense* contributed to the study protocol and questionnaire.

Statistical analyses

Descriptive analyses of the clinical characteristics and outcomes are based on all children who had head size <0.4th percentile (-2.67SD) and were reported to the study during the surveillance period. We included children with a head circumference between -3SD and -2.67SD (i.e. below 0.4th percentile) in these *clinical analyses* as, following standard clinical practice, they were being managed by UK and Irish clinicians as severe microcephaly.

To enable comparison across different countries and studies, we based our estimate of the *incidence* of new diagnoses of severe microcephaly only on confirmed cases with a **head size <-3SD** reported to the study between 01 November 2017 and 31 October 2018 (12 months). We excluded cases reported in October 2017, which was the first month of surveillance, as prevalent cases were more often reported during this run-in period. The mid-year population estimates of children aged 0-1 year old in 2018 in the UK and RoI were used as the denominators; the total mid-year population estimate was 806 792.^{13 14} Relative risk of severe microcephaly by sex, ethnicity, socio-economic deprivation, region and birth gestation was calculated for children in England only (n=40) as denominator data were not available for other countries.¹⁵⁻¹⁷

RESULTS

Cases reported

Paediatricians reported 167 potential cases and completed clinical questionnaires for 140 (84% response rate; Figure 1). Eighty-one cases were excluded: 11 duplicates, 34 diagnosed outside the surveillance period, five diagnosed after age 12 months, and 31 with head size \geq -0.4th percentile. In this last group, reporting was precipitated by neurodevelopmental problems (n=28), microcephaly risk factors (n=11) or moderate microcephaly (<-2SD; n=11).

Fifty-nine children met the case definition for inclusion (head size <-2.67SD or <0.4th percentile) during the 13 month period of case reporting from 01 October 2017 to 31 October 2018; after removal of deaths, follow-up information was available on 37 survivors at one year and 26 survivors at two years of age (Figure 1). Of these 59 children, 54 were from England, 31 (51%) were girls, 24 (41%) were born preterm (<37 weeks gestation) and 48 (81%) were of white or Asian ethnicity (Table 1).

Incidence and relative risk

The annual incidence of severe microcephaly in the UK and RoI was 5.45 (95% confidence intervals [CI] 3.96, 7.32) per 100 000 infants, based on 44 infants with a head size <-3SD diagnosed between 01 November 2017 and 31 October 2018 (12 months).

Children from England had twice the risk of severe microcephaly as the rest of the UK and RoI combined (England 6.27 [95%CI 4.48, 8.54]; UK/RoI 2.37 [95% CI 0.65, 6.06]; relative risk [RR] 2.7 [95% CI 1.9, 3.6]). Within England, there was marked regional variation; North East and Yorkshire had a risk significantly higher than other regions (Table 2). A higher risk of severe microcephaly was also associated with preterm birth (RR 7.7 [95% CI 3.8, 15.1]) and Asian ethnicity (RR 3.6 [95% CI 1.6, 7.8] compared with white ethnicity). Most (n=10; 72%) affected British Asian infants were of Pakistani origin (Table 1). There was no increased risk associated with sex or socioeconomic deprivation.

Clinical presentation

Children were diagnosed in the first year of life at a median age of 52 days (interquartile range [IQR] 0,

118 days); microcephaly was recognised on the first day of life in 19 (32%) children. The diagnosis was suspected at routine child health surveillance (including prenatal screening) in 31 children (median age at diagnosis 14 [interquartile range (IQR) 0, 91] days; mean head circumference -4.2 SD), because of clinical signs in 23 children (median age 95 [IQR 1, 227] days; mean head circumference -3.3 SD) and for other reasons, such as family history, in 5 children.

There were concerns about 37 (63%) babies in the postnatal period; 8 required resuscitation at birth and 32 were admitted to neonatal intensive or special care units. Intra-uterine growth retardation (IUGR) was reported in 30 (51%) infants and 18 had microcephaly or brain abnormalities on fetal ultrasound (eTable 1). Twenty-three (39%) children had other congenital anomalies in addition to microcephaly (eTable 2).

Clinical investigations and management

Almost all ($n=57$; 97%) children had brain imaging (MRI, ultrasound and/or CT scan) at diagnosis or follow-up and 49 had >1 scan. Forty-four (77%) children had at least one abnormal scan result (eTables 1 and 3). Twenty-two children had an EEG and 18 had at least one abnormal EEG.

Thirty-five children underwent genetic testing and 11 (31%) had genetic/chromosomal abnormalities. Twenty-five children were tested for one or more congenital infections and in five (20%) cases a congenital infection was considered the cause of microcephaly (eTable 4). Twenty-five children underwent metabolic testing; four (16%) had partially abnormal results but none were the cause of the microcephaly.

Children were referred to a median of eight (IQR 3, 10) specialist clinicians for further assessment or care (eFigure 2). Twenty-nine children were started on regular medications (median 3 [IQR 1, 4] medications), most frequently an anti-epileptic (eTable 5).

Aetiology

The primary cause of microcephaly was determined for 48 (81% of 59) children (Table 3). Genetic causes were responsible for 35 (59% of 59) cases, congenital infections for 5 (8% of 59) and ischaemic/hypoxic brain injury for 6 (10% of 59). Of 35 children with genetic causes, 10 had a confirmed chromosome or gene abnormality. A genetic cause was not confirmed, but was likely in a further 25 children, including 10 with

multiple congenital anomalies and 6 who had a sibling with microcephaly (Table 3). Children of British Pakistani ethnicity were over-represented among the group of children with affected siblings and/or consanguineous parents (first or second cousins).

Thirteen children were exposed to known maternal health-associated risk factors in utero, including gestational diabetes, hypothyroidism, hypertension, phenylketonuria and febrile illness (eTable 6). Many children had associated conditions that were not the primary cause of the microcephaly.

Outcomes

By study completion, 10 children had died, five had been discharged from care with normal head growth and neurodevelopment, and the others remained under clinical care (Figure 1).

Most children (n=55; 93%) experienced problems in at least one area of neurodevelopment (Table 4). Between birth and 2 years, 39 (66% of 59) children had delayed motor milestones, and 36 (61% of 59) had neurological abnormalities. Forty children experienced feeding problems by 1 year of age. Visual impairment (VI) was diagnosed in 22, eye abnormalities in 23, hearing loss (HL) in 14 and epilepsy in 24 children by two years of age.

Of 37 children followed up at 1 year of age, 17 (46%) had developmental impairment (Table 4). At two years, 26 children remained under follow up; of these, 19 had delayed speech, 19 had delayed gross motor skills, nine (had delayed fine motor skills, 12 had VI (five were certified sight impaired) and eight children had HL (two wore hearing aids).

DISCUSSION

The annual incidence of severe microcephaly is 5.5 per 100 000 babies born in the UK and RoI. As this does not include miscarriages, stillbirths or pregnancy terminations associated with microcephaly, it is likely to be an underestimate of the true incidence rate. The risk of severe microcephaly is twice as high in England as the other nations, three times higher in babies of British Asian ethnicity compared with white infants and seven times higher in babies born preterm. The most common cause is genetic but, importantly, the cause remains unknown in around one-fifth of infants. Over 90% of affected babies had evidence of neurodevelopmental delay by two years, 40% had additional congenital anomalies and 17% died. Most children underwent multiple investigations and each child was referred to on average eight specialists. These findings demonstrate the significant health and care burden represented by this group of children who require lifelong access to a broad range of support services.

Severe microcephaly incidence in our study was lower than previous UK reports⁷⁻⁹ but consistent with population-based evidence from north America^{5 18}, Australia⁴, and Europe.¹⁹ Reported microcephaly incidence shows considerable variation^{19 20} related to ascertainment methods^{4,5 7 21-23}, inconsistent case definitions and inaccurate head measurements. We validated head measurements against centile charts and excluded children who did not meet our rigorous case definition. These incidence variations underline the importance of standardised case definitions and validated reporting to enable secular and geographical comparison. Robust data are essential for birth defects monitoring to allow recognition of rising incidence denoting new and emerging causal factors, like Zika virus.²⁴

We identified a high relative incidence of severe microcephaly in specific risk groups, including British Asian infants. As a higher proportion of births in England are to women of British Asian ethnicity compared with the other nations, this may have contributed to these differences. Infants of Pakistani origin were over-represented among those with affected siblings or consanguineous parents. A strong association between Pakistani ethnicity and neurodegenerative disorders has been reported²⁵ and autosomal recessive primary microcephaly is more common in consanguineous Arab and Asian populations.²⁶ While it seems possible that consanguinity contributed to higher frequency in the British

Pakistani population, the impact of endogamy (preference for within community marriage) cannot be ruled out.²⁷

Consistent with other reports⁴⁻⁶, we found most children had a genetic cause for severe microcephaly. This was confirmed by genetic testing in 17% but we also considered affected siblings or microcephalic syndromes to be highly suggestive of genetic causes, resulting in 60% cases attributable to genetic causes. Fewer children in our study had no known cause for their microcephaly compared to previous studies⁴⁻⁶, due to our use of a systematic classification system and collection of clinical information throughout follow up. As many children had multiple risk factors for microcephaly, we developed a hierarchy of primary and associated causes, so laboratory evidence of congenital infection took precedence over history of maternal alcohol use, and we reported 'secondary' causes where relevant. Abnormal brains scans were found in 77% of children in our study; this high rate is comparable with other reports, which range from 39% to 80%.^{1,4-6} Taking a systematic clinical approach to investigating microcephaly is fundamental to understanding risk factors and implementing effective prevention.

Microcephaly is a lifelong condition therefore clinical management is targeted at optimising neurodevelopment and managing comorbidities. Current evidence-based recommendations¹ for managing microcephaly are based on limited evidence, and active surveillance studies are contributing fundamental data to inform future clinical guidelines. Many children in our study had multimorbidity (≥ 2 long-term conditions), which is associated with higher mortality and more frequent hospital admission. Microcephaly is associated with vision and hearing anomalies^{1 28 29 30} and Dolk reported a strong relationship between low IQ and severe microcephaly.³¹ Interestingly five children in our study were discharged with 'normal' head *growth* by two years of follow-up, and clinicians reported that these children had small head size without any evidence of neurodevelopmental abnormalities. This suggests that they fell into the group of children whose head size is at the lower end of the normal population distribution and where long-term clinical monitoring is not required.

The high number of specialist referrals for each child in our study confirms the need for multidisciplinary input and underlines the significant costs that multimorbidity places on NHS services. Timely

identification of the cause, referral for genetic counselling, and provision of care are essential to support affected children. All infants with microcephaly should have investigations for associated neurodisability and sensory impairments, and regular monitoring for neurodevelopmental abnormalities throughout the early years. It is especially important for clinicians to be aware that the relationship with family history and consanguinity means a disproportionately heavy burden of care falls on families who have more than one affected infant with multiple complex needs.

Strengths of this study are the high case ascertainment, achieved through active surveillance, and rigorous application of the case definition to avoid bias. Our systematic approach to classifying cause supports methodological robustness and reproducibility. Good follow up and outcome data at age two has allowed us to describe a wide range of neurodevelopmental problems that were not detected at diagnosis. A limitation was our reliance on the BPSU as our single source for case ascertainment, however monthly submissions to the BPSU were achieved by 94% of paediatricians and questionnaire response rates were high. Case reports that could not be validated due to a lack of clinical details were excluded, which may have contributed to a lower incidence rate. We also relied on data extraction from routine medical records, which meant some clinical information was incomplete and, in particular, we lacked any detailed data from genetic testing.

Early detection is vital for implementing timely and appropriate interventions for children affected by severe microcephaly and care and support to families. Encouraging routine recording of head circumference by health professionals during the first year of life could improve timeliness of identification, while developing consensus guidelines on management would improve the quality of care. It is vital that we compare the findings from this and other active surveillance studies with birth defect monitoring systems^{8 32} to validate incidence rates from different sources and establish a baseline for routine reporting that will enhance its effectiveness as an early warning system for unexpected increases.

Table 1 – Characteristics of children with severe microcephaly in UK and Republic of Ireland (n=59 cases)

	Cases		(95%CI)
	N	%	
Sex			
Female	30	51%	38%, 64%
Male	29	49%	36%, 63%
Ethnic group			
White	34	58%	44%, 70%
Asian or Asian British	14	24%	14%, 37%
<i>Asian or British Asian – Pakistani</i>	10	-	-
<i>All other Asian or British Asian</i>	4	-	-
Mixed or multiple ethnic groups	3	5%	1%, 14%
Other ethnic group	5	8%	3%, 19%
Missing	3	5%	1%, 14%
Gestational age at birth			
Term (≥ 37 weeks)	35	59%	46%, 72%
Preterm (< 37 weeks)	24	41%	28%, 54%
<i>Preterm (32-< 37 weeks)</i>	13	-	-
<i>Very preterm (28-32 weeks)</i>	3	-	-
<i>Extremely preterm (< 28 weeks)</i>	8	-	-
Birth type			
Singleton	54	92%	81%, 97%
Multiple	3	5%	1%, 14%
Not Known	2	3%	0%, 12%
IMD quintile			
1 – least deprived	6	10%	4%, 21%
2	7	12%	5%, 23%
3	10	17%	8%, 29%
4	14	24%	14%, 37%
5 – most deprived	15	25%	15%, 38%
Missing	7	12%	5%, 23%
Birth anthropometry (missing=16)^a	<i>median</i>	<i>IQR</i>	
Head circumference (Z-score)	-3.4	-4.5, -2.0	
Birthweight (Z-score)	-1.3	-2.1, -0.1	
Length (Z-score)	-2.5	-3.0, -2.0	
Anthropometry at diagnosis (missing=0)	<i>median</i>	<i>IQR</i>	
Head circumference (Z-score)	-3.7	-4.5, -3.1	
Weight (Z-score)	-1.8	-2.4, -1.1	
Length (Z-score)	-1.4	-2.6, -0.9	
Age at microcephaly diagnosis	<i>median</i>	<i>IQR</i>	
Age (days)	52.0	0, 118.0	

^a 27 infants had a head circumference more than -2.67SD below the mean

Table 2 – Relative risk of Severe Microcephaly in infants aged up to one year in England only (n=40)

	N	Cases	Incidence ^a	RR
		% (of 40)	per 100,000	(95%CI)
Sex				
Female	17	43%	5.47	Reference
Male	23	58%	7.03	1.28 (0.81, 1.93)
Ethnic group				
White	22	55%	4.53	Reference
Asian or British Asian	11	28%	16.38	3.62 (1.58, 7.78)
Other/Missing	7	18%	^b	-
Area deprivation (quintile)				
1 – least deprived	4	10%	4.2	Reference
2	5	13%	4.6	1.09 (0.23, 5.48)
3	7	18%	5.7	1.36 (0.35, 6.34)
4	12	30%	8.2	1.95 (0.59, 8.29)
5 – most deprived	11	28%	6.3	1.51 (0.45, 6.50)
Missing	1	3%	-	-
NHS Regions				
London	5	13%	4.2	Reference
South East	4	10%	4.3	1.02 (0.28, 2.62)
Midlands	5	13%	4.3	1.03 (0.33, 2.39)
North West	5	13%	6.3	1.50 (0.49, 3.49)
East of England	5	13%	7.0	1.64 (0.53, 3.84)
South West	5	13%	9.3	2.20 (0.71, 5.13)
North East & Yorkshire	11	28%	12.3	2.89 (1.44, 5.17)
Gestational age at birth				
Term (≥37 weeks)	24	60%	4.04	Reference
Preterm (<37 weeks)	16	40%	31.18	7.71 (3.83, 15.13)

^a sources of denominator data for: sex¹³, ethnicity¹³, area deprivation¹⁶, gestational age¹⁷, NHS regions¹⁵

^b incidence cannot be calculated as no denominator for missing data

Table 3 – Detailed causes of microcephaly (n=59)

	Cases N (%)
Genetic causes	
Confirmed	10 (17%)
COL4A1 mutation	2
Metabolic (genetic)/leukodystrophy	1
Aicardi syndrome	1
CASK gene duplication	3
TRAPPC12 gene mutation	1
Dandy Walker syndrome	1
Unspecified gene mutation associated with microcephaly	1
Probable	20 (34%)
Affected siblings ^a	6
Syndrome ^b	2
Multiple anomalies	10
Clinical report ^c	2
Possible	5 (8%)
Consanguinity	3
Hypopituitarism	1
Cortical hypodevelopment	1
Congenital infections	5 (8%)
Congenital cytomegalovirus (CMV)	3 ^d
Congenital toxoplasmosis	2 ^d
Congenital herpes simplex virus (HSV)	1
Ischaemic/ Hypoxic	6 (10%)
Pre/perinatal stroke/haemorrhage (infant)	4
Pre/perinatal hypoxia (maternal stroke; placental abruption)	2
Maternal/pregnancy exposures^e	1 (2%)
Craniosynostosis	1 (2%)
Cause undetermined	11 (19%)

^a 2 children had affected siblings and multiple anomalies

^b phenotypic or genetic syndrome but not previously associated with microcephaly

^c clinician reported genetic cause but did not provide further details

^d 1 child had both CMV and toxoplasma infection.

^e exposure to alcohol, drug, medication or toxin associated with microcephaly

Table 4: Neurodevelopmental abnormalities at diagnosis and follow-up

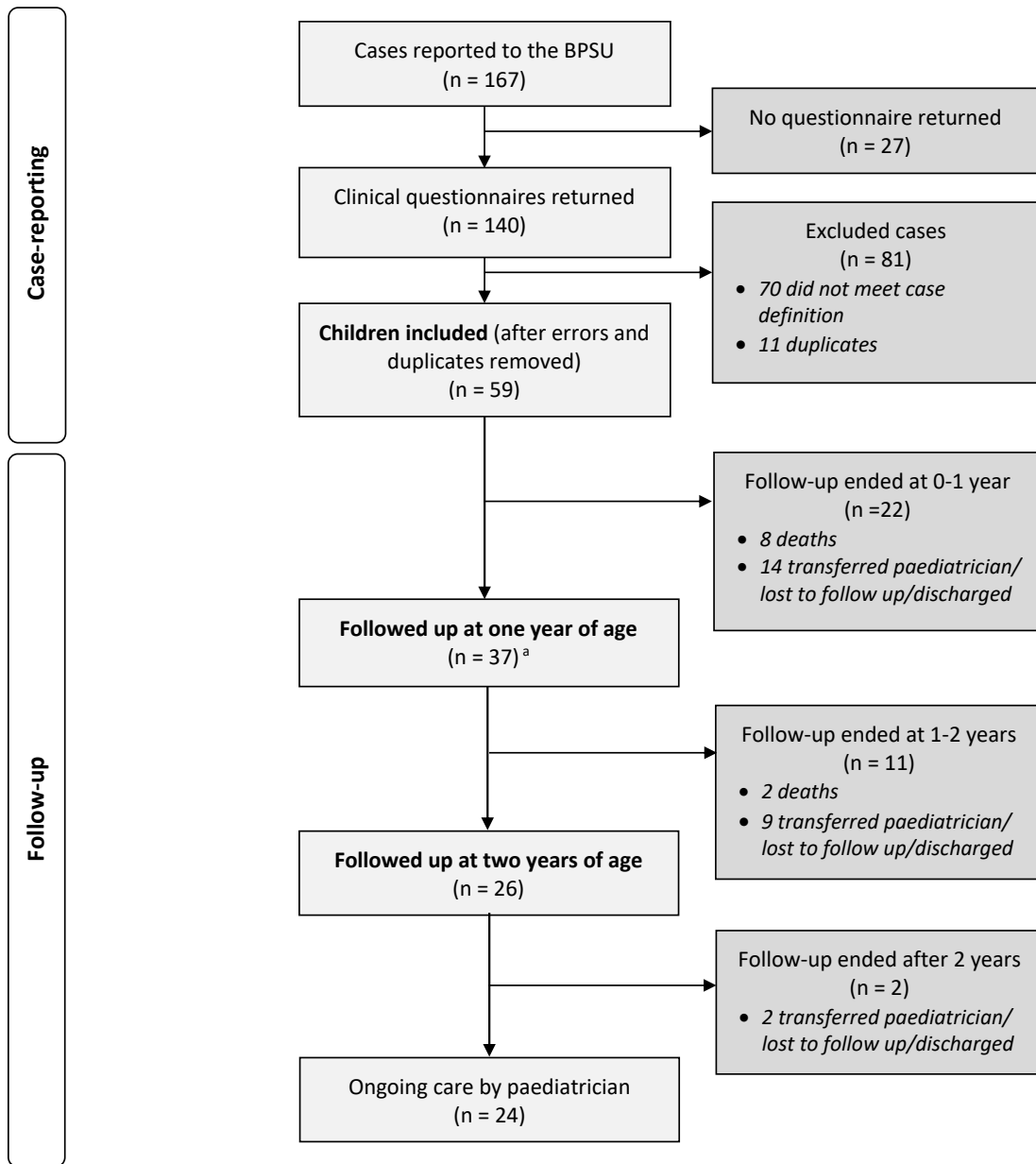
Cumulative neurodevelopmental abnormalities at diagnosis, 1 year and 2 years				N=59
	No problems	Problems noted (cumulative)		
		By diagnosis	By age 1 year	By age 2 years
Feeding problems	19	19	40	-
Delayed motor milestones	20	22	38	39
Abnormal visual responses ^a	37	17	19	22
Eye abnormalities ^a	36	18	22	23
Hearing loss	45	11	12	14
Seizures or epilepsy	35	13	22	24
Abnormal neurological examination	23	28	35	36
No problems	4	-	-	-
Neurodevelopmental abnormalities reported at 1 year				N=37
Developmental impairment				17 (46%)
Neurodevelopmental abnormalities reported at 2 years				N=26
Speech	No problems reported			7 (27%)
	Speech and language delay			19 (73%)
	<i>Using words</i>			5 (19%)
	<i>Babbling</i>			9 (35%)
	<i>Signs/gestures</i>			1 (4%)
	<i>No vocalisation or signs</i>			4 (15%)
Gross motor skills	No problems reported			7 (27%)
	Delayed motor skills			19 (73%)
	<i>Walks without aid</i>			3 (12%)
	<i>Stands without support</i>			2 (8%)
	<i>Sits without support</i>			5 (19%)
	<i>Unable to sit without support</i>			9 (35%)
Fine motor skills	No problems reported			17 (65%)
	Delayed fine motor skills			9 (35%)
Vision and eye problems	No problems reported			14 (54%)
	Eye abnormalities without VI			4 (31%)
	Vision impairment (VI)			5 (19%) ^b
	Cerebral visual impairment (CVI)			7 (27%) ^c
	<i>Certified sight impaired</i>			5 (19%)
Hearing loss	No problems reported			18 (69%)
	Hearing loss reported			8 (31%)
	<i>Hearing aids</i>			2 (8%)

^a 13 children had both ocular and vision abnormalities at 2 years

^b 3 children also had eye abnormalities

^c 1 child also had eye abnormalities

Figure 1 – Cases reported and followed up to two years of age (n=59)



^a Although follow-up data was not provided contemporaneously at 1 year of age for 5 children, this data was provided retrospectively at 2 years of age.

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Authors' Contributions

RLK, JR, ALS, JS, NO conceived the study, developed the study protocol and methodology and obtained funding. RLK, MAS and CRB collected and prepared the data and undertook preliminary analyses. All authors contributed to data analysis and interpretation. RLK and ALS drafted the manuscript, and all authors contributed to, reviewed and approved the final manuscript.

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Transparency Declaration

The lead author and guarantor of this manuscript, Dr Rachel L Knowles, affirms that this manuscript is an honest, accurate and transparent account of the study being reported; no important aspects of the study have been omitted; and any discrepancies from the study as originally planned have been explained.

Competing Interest Statement

No authors have any competing interests to declare.

Data Sharing Statement

The data used in this study were collected from medical records and included indirect identifiers. Collection and analysis of this data without consent was supported under section 251 of the Health and Care Act. As the data come from a small population affected by a rare disease and cannot be fully de-identified, we are not able to share an individual-level patient dataset. However extensive aggregated data tables are provided in this paper and in the online tables.

What is already known on this topic

- Severe microcephaly is associated with neurodisability that has lifelong impact on individuals and their families.
- Reported incidence of microcephaly from observational studies and congenital anomaly reporting systems varies widely and the true burden of disease is unclear.
- Incomplete understanding of the causes of severe microcephaly presents a challenge to implementing effective prevention and clinical management.

What this study adds

- Contemporary national incidence of severe microcephaly for the UK and Ireland to enable future increases due to emerging causes to be rapidly identified and addressed.
- Severe microcephaly was due to genetic causes in 60% cases and can represent a significant burden for individual families due to genetic clustering of cases.
- Neurodevelopmental outcomes at two years are abnormal in over 90% of infants with severe microcephaly, including critical deficits in vision, hearing, speech and motor skills.

How this study might affect research, practice and policy

- Study findings should inform the development of consensus clinical guidelines for microcephaly focused on standardising aetiological investigations and optimising long-term management of associated multimorbidity.
- The study highlights the benefit of addressing the potentially preventable causes underlying one-fifth of microcephaly cases, including congenital infections, pregnancy exposures and hypoxic/ischaemic brain injury.

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SUPPLEMENTARY ONLINE TABLES AND FIGURES

eTable 1 – Clinical investigations (n=59)

Scans		
At least one abnormal scan	44 children	
At notification	Total children scanned (N)	Abnormal result (N [% of all scans])
CT	10	7 (70%)
MRI	39	33 (85%)
USS	38	24 (63%)
At follow-up	Total children scanned (N)	Abnormal result (N [% of all scans])
CT	6	3 (50%)
MRI	21	16 (76%)
EEG		
At least one abnormal EEG	18 children	
At notification	Total children investigated (N)	Abnormal result (N [% of all EEGs])
EEG	18	11 (61%)
At follow-up	Total children investigated (N)	Abnormal result (N [% of all scans])
EEG	15	11 (73%)
Fetal USS		
Abnormal fetal USS	23 children	N (% of 59 babies)
	<i>Microcephaly</i>	11 (19%)
	<i>Brain abnormality</i>	7 (12%)
	<i>Other abnormality</i>	5 (8%)

eTable 2 – Associated congenital anomalies (n=23)

	N
Congenital heart disease	6
Multiple anomalies	6
Hand anomaly	3
Endocrine disorder	2
Genitourinary anomaly	2
Cleft lip and palate	2
Talipes equinovarus	2
Gastrointestinal anomaly	1
Dysmorphic features	1
Skin condition	1
Bone condition	1

23 children were affected but individual anomalies do not add up to 23 as some children had >1 anomaly

eTable 3 – Details of Scan and EEG results

Scan results	
	N=59
Cortical malformation	18
Enlarged brain ventricles	13
Cerebellar abnormalities	12
Decreased brain volume	10
Corpus callosum abnormalities	9
Brain calcification	6
Abnormal myelination	6
Other skull/brain abnormalities	17
EEG results	
	N=59
Abnormal cortical activity	7
Seizure activity	10

eTable 4 – Clinical investigations

Infection	Tested (n)	Positive (n)
CMV	21	4
Toxoplasmosis	15	2
Rubella	13	0
HSV	8	1
Syphilis	3	0
Varicella Zoster	3	0
Hepatitis B	3	0
Zika	2	0
HIV	1	0
Metabolic tests	Tested (n)	Abnormal results (n)
Metabolic tests	25	4 (no metabolic causes of microcephaly identified)

eTable 5 – Regular medication being taken by 29 children

Type of medication	Number of children reported to be taking medication type
Anti-epileptics (e.g. phenobarbitone, levetiracetam, sodium valproate, carbamazepine, diazepam, vigabatrin)	12
Antacid (e.g. ranitidine, omeprazole, gaviscon)	10
Vitamins or supplements (e.g. iron, phosphate, vitamin B, vitamin E, folate, multivitamins)	9
Diuretics (e.g. spironolactone, furosemide)	8
Steroids (e.g. hydrocortisone, fludrocortisone, dexamethasone)	6
Antibiotic/antiviral (e.g. cephalexin, acyclovir, valgancyclovir)	3
Other (e.g. baclofen, desmopressin, ursodeoxycholic acid, levothyroxine, sildenafil)	8

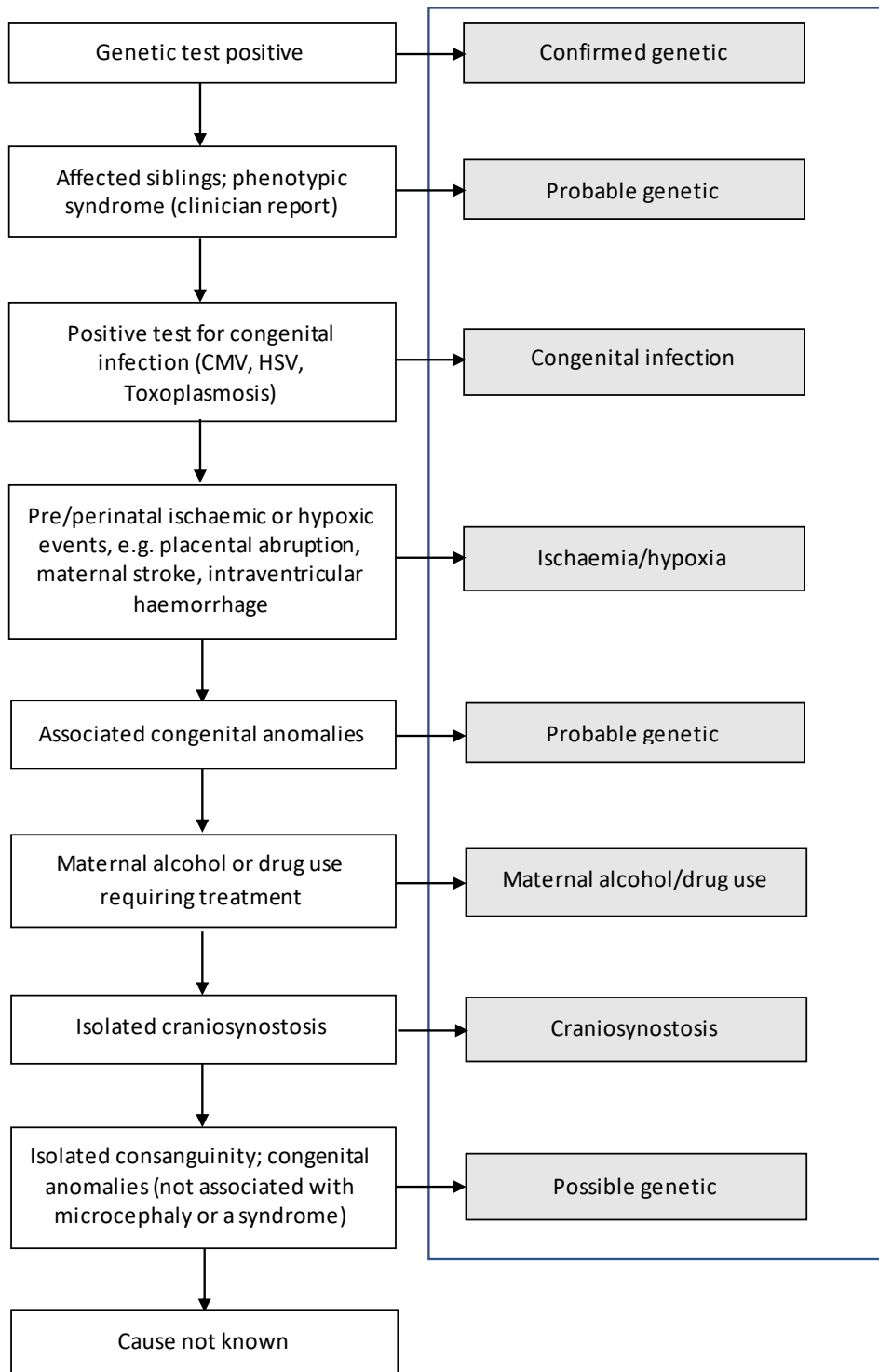
eTable 6 – Primary cause and associated conditions (n=59)

Cause	Associated conditions							Total
	Alcohol or drug use	Craniosynostosis	Multiple anomaly	Consanguinity	IUGR ^a	Smoking	Maternal ill-health ^b	
Confirmed Genetic	0	3	7	1	5	1	1	10
Probable Genetic	0	4	13	9	12	3	4	20
Possible Genetic	0	0	1	3	3	0	1	5
Congenital Infection	3	0	1	0	2	1	0	5
Ischaemic/Hypoxic	0	0	1	1	2	1	2	6
Maternal alcohol/ drug use	1	0	0	0	0	0	0	1
Craniosynostosis	0	1	0	0	0	0	0	1
Cause undetermined	0	0	0	0	6	0	5	11
Total	4	8	23	14	30	6	13	59

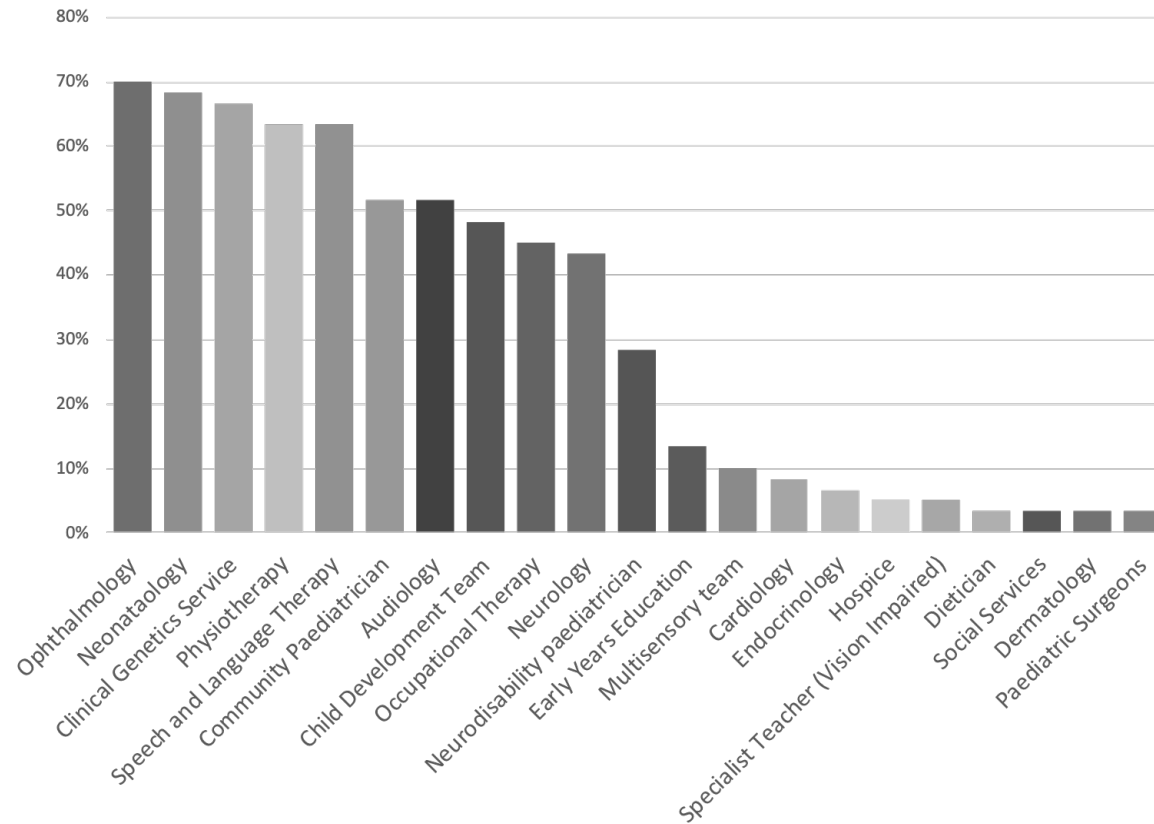
^a IUGR = intrauterine growth retardation

^b includes maternal stroke, hypertension, diabetes, epilepsy, febrile illness during pregnancy

eFigure 1: Hierarchical model for assigning cause



eFigure 2: Specialist Referrals (as a percentage of 59 children referred to each service)



One referral was also made to each of the following: Neurosurgery, Cleft lip and palate team, Community nurse, Paediatric Infectious Disease, Immunology, ENT, Orthopaedic surgeons, Gastroenterology, Renal service

