

Keywords: childhood brain tumour; infectious disease; social contact; epidemiology; children

Patterns of exposure to infectious diseases and social contacts in early life and risk of brain tumours in children and adolescents: an International Case–Control Study (CEFALO)

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Background: Infectious diseases and social contacts in early life have been proposed to modulate brain tumour risk during late childhood and adolescence.

Methods: CEFALO is an interview-based case–control study in Denmark, Norway, Sweden and Switzerland, including children and adolescents aged 7–19 years with primary intracranial brain tumours diagnosed between 2004 and 2008 and matched population controls.

Results: The study included 352 cases (participation rate: 83%) and 646 controls (71%). There was no association with various measures of social contacts: daycare attendance, number of childhours at daycare, attending baby groups, birth order or living with other children. Cases of glioma and embryonal tumours had more frequent sick days with infections in the first 6 years of life compared with controls. In 7–19 year olds with 4+ monthly sick day, the respective odds ratios were 2.93 (95% confidence interval: 1.57–5.50) and 4.21 (95% confidence interval: 1.24–14.30).

Interpretation: There was little support for the hypothesis that social contacts influence childhood and adolescent brain tumour risk. The association between reported sick days due to infections and risk of glioma and embryonal tumour may reflect involvement of immune functions, recall bias or inverse causality and deserve further attention.

Brain tumours are the second most frequent type of childhood cancer with a high mortality rate and a high frequency of long-term morbidity and psychosocial sequelae (Reimers *et al*, 2003). The annual incidence rates range from 20 to 40 cases per million children, with the highest rates reported in the Nordic countries (Peris-Bonet *et al*, 2006; Lantering *et al*, 2009; Schmidt *et al*, 2011).

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Received 11 December 2012; revised 26 March 2013; accepted 29 March 2013; published online 7 May 2013

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Better knowledge of the aetiology of childhood and adolescent brain tumour (CABT) for primary prevention strategies is therefore important.

A review of epidemiologic studies by Schüz and Kaatsch, 2002 suggests that infections could initiate or modify the risk of CABT similar to the infection hypothesis that has been proposed for childhood acute lymphoblastic leukaemia (Schüz *et al*, 1999; Roman *et al*, 2007; Kamper-Jorgensen *et al*, 2008). Exposure to infectious agents early in childhood could cause an abnormal immune response when exposed to infectious diseases later in childhood (Kinlen, 1995; Greaves, 2006).

Some studies have not found an association between infectious agents and CABT (Birch *et al*, 1990; Little, 1999; McKinney *et al*, 1999). Most of these studies, however, had small sample sizes and therefore low statistical power to detect an association and other studies have found an association between risk of CABT and various measures of infectious diseases (Linet *et al*, 1996; Dickinson *et al*, 2002; Shaw *et al*, 2006) or indications of an association with exposure to polyoma viruses (SV40, JCV and BKV) (Bunin, 2000; Vilchez and Butel, 2003; Khalili *et al*, 2003).

Children's exposure to infectious diseases in early childhood is most commonly through contact with other children (Ma *et al*, 2009). Studies have shown that attending daycare increases a child's risk of getting infectious diseases (Thrane *et al*, 2001; Kamper-Jorgensen *et al*, 2006; von Linstow *et al*, 2008), indicating that social contacts could reflect the general exposure to infections. Studies investigating the relationship between social contacts and CABT have, however, only found little or no evidence of an association (Shaw *et al*, 2006; Harding *et al*, 2009; Schmidt *et al*, 2010).

To evaluate the infection hypothesis for CABT further, we investigated the patterns of infectious diseases and social contacts in early life in relation to risk of developing a brain tumour during late childhood and adolescence in the CEFALO study.

MATERIALS AND METHODS

The CEFALO study is a multinational case-control study conducted in Denmark, Norway, Sweden and Switzerland, with the primary aim to investigate the possible association between CABT risk and mobile phone use and other relevant exposures (Aydin *et al*, 2011).

Case and control ascertainment. Eligible cases were children diagnosed with a primary intracranial brain tumour (Aydin *et al*, 2011) aged 7–19 years at the date of diagnosis. The study period was from 1 January 2004 until 1 August 2008, but varied slightly across the four countries (Denmark: January 2004–April 2008; Sweden: April 2004–August 2008; Switzerland: May 2004–2008; Norway: September 2004–August 2008).

To attain complete case ascertainment, cases were identified both at hospitals and in country-specific disease registries (the Danish National Cancer Registry (Tulinus *et al*, 1992; Storm *et al*, 1997); Danish Childhood Cancer Registry, Danish Pathology Registry, Danish National Patient Registry, the Swedish Regional Cancer Registries (Barlow *et al*, 2009), the Cancer Registry of Norway (Larsen *et al*, 2009) and Swiss Childhood Cancer Registry). Date of diagnosis was defined as date of first diagnostic imaging confirming a CABT.

Two controls per case were randomly selected from nationwide population registries in Scandinavia and in Switzerland from communal registries, and were individually matched by age (Denmark, Switzerland and Sweden: month of birth; Norway: year of birth), gender and region. Exposure of controls was censored at the date of diagnosis of the matched case.

Subjects diagnosed with Recklinghausen neurofibromatosis (12 cases) and tuberous sclerosis (one case) were excluded as their aetiology is genetic. Cases and controls with severe autism, severe

mental retardation or complete deafness before the date of diagnosis were also excluded (two cases and two controls). In addition, families with insufficient language skills to complete an interview were excluded (15 cases and 36 controls). The study was approved by the National Data Protection Boards and ethical committees in all participating countries.

Data collection. Cases diagnosed before June 2006 (Norway: December 2007) and corresponding controls were included retrospectively. All other cases were included prospectively. A structured personal interview was performed with the child and one or preferably both parents by a trained interviewer during the time period 2006–2009. For ethical reasons, the interview was conducted at least 6 months after the date of diagnosis. Questionnaire translations were validated and pilot tested in all participating countries.

Variables and analysis strategy. We used the following variables as measures of social contacts and of exposure to infectious disease: living with other children before 6 years of age of index child (yes/no); birth order (1st born/>1st born); attending daycare in first year of life (yes/no) and before 6 years of age (yes/no); attending baby groups (at least once a week) within the first year of life (yes/no); mean number of days where child's general condition was appreciably affected by infectious disease (once or less per month, 2–3 days per month, 4 days or more per month) at different ages (<1, 1–<3, 3–<6 years), calculated as a weighted average of answers provided per semester for the first 3 years of life and for the next 3 years of life combined (see Supplementary Appendix 1 online). The list of infectious diseases included: cold, fever without known cause, middle ear infection, tonsillitis, bronchitis, pneumonia, skin infection, urinary tract infection, stomach flu and others (e.g. whooping cough, 3-day fever, scarlet fever). For each child we also assessed cumulative daycare exposure by calculating total daycare childhours (categorised into quintiles) during the first 6 years of life as used by Ma *et al* (2002): *Number of months attending a specific daycare* × 4.35 (average number of weeks per month) × hours per week at daycare × number of children at daycare. The childhours were cumulated over all daycare facilities attended during the time period of interest. As early brain tumour-related symptoms might have influenced daycare attendance, all daycare information for the past 2 years before diagnosis or end of exposure date were disregarded (only relevant for the 7 and 8 year olds in our study). In addition, information on allergic conditions (yes/no) was available for all children, defined as having at any time before diagnosis of the matched case: doctors diagnosis of asthma, hay fever or eczema; or wheezing or whistling in the chest; itchy/watery eyes and sneezing/runny/blocked nose not in connection with a cold or the flu; or rash of folds of elbows, knees, front of ankles, under buttock or around neck, eyes or ears.

For statistical analysis, tumours were classified as: 'Glioma' (astrocytomas, other gliomas), 'intracranial embryonal CNS tumours' (including primitive neuroectodermal tumours (PNET)) and 'Others' (ependymoma, other specified intracranial neoplasms, unspecified intracranial neoplasms).

Data were analysed by conditional logistic regression in SAS (version 9.2; SAS Institute Inc., Cary, NC, USA). Relative risk estimates were expressed as odds ratios (OR) with associated 95% confidence intervals (CI). Highest attained education of parents as a proxy for socioeconomic status was included in the models as potential confounder, but did not alter the risk estimates and was therefore omitted from the final model (data not shown).

RESULTS

In total, we invited 423 brain tumour cases and 909 controls and their families to participate in the CEFALO study. We interviewed

352 cases and 646 controls with participation rates of 83 and 71%, respectively. The most common reasons for non-participation are shown in Table 1.

The largest group of CABT in the study was glioma (55%) followed by ‘other tumours’ (28%) and intracranial embryonal tumours/PNET (18%) (Table 1). This corresponds to the overall distribution of tumour types in the Nordic countries (Schmidt *et al*, 2011).

Overall there were slightly more boys than girls in the study. Two-thirds of the participating children and adolescents were between age 7 and 14 years, while only one third was between 15 and 19 years (Table 1). A large proportion of children attended daycare before 6 years of age (87%). The majority of children attended baby groups (72%) and most (94%) of the index children were living together with siblings or other children. Regarding monthly number of days with infectious disease during the first 6 years of life, the majority of children were reported to have infectious disease once or less per month (67%), 20% 2–3 days per month and 9% 4 days or more per month.

Overall, no OR of any measure of social contacts was statistically significantly increased or decreased (Table 2); this did not change when stratifying by gender (data not shown). Furthermore, no changes in ORs were observed when controlling for allergy (never/ever allergy) (data not shown). However, a tendency of slightly increased risks were found for glioma and total childhours (only significant for fourth quintile; OR: 3.39; 95% confidence interval (CI): 1.54–7.46), living with other children before 6 years of age (OR: 1.64; 95% CI: 0.73–3.67) and attending baby groups during the first year of life (OR: 1.47; 95% CI: 0.95–2.28). Such a pattern was not observed for other CABT.

With regard to infectious disease (Table 3), the OR for all CABT types combined was 1.27 (95% CI: 0.89–1.80) for children having 2–3 sick days per month in the 0–6 years of age and 1.87 (95% CI: 1.19–2.97) for children with 4 or more sick days per month (0–6 years) compared to children with one sick day or less per month (Table 3). Girls tended to have higher risk estimates for CABT than boys (data not shown). Controlling for diagnosed allergy did not alter the risk estimates. When stratifying by tumour type, increases were restricted to glioma and embryonal CNS tumours: an average of 4 or more monthly sick days at ages 0, 0–2, 3–5 or 0–5 years was associated with significantly increased risk of glioma. The observed risk was of similar magnitude, regardless of period of exposure, with the highest risk seen when looking at sick days over the first 6 years of life (OR: 2.93; 95% CI: 1.57–5.50). There was a tendency for similar increases for embryonal CNS tumours, the risk estimates tended to be slightly lower than for glioma, except when looking at the first 6 years of life combined where the OR was 4.21 (95% CI: 1.24–14.30), numbers were, however, small and the CI very wide.

For other CABTs, no indication of a risk increase with self-reported number of sick days was observed (Table 3).

We tested for interaction between total daycare childhours and number of days of infections (0–<6 years), as well as for birth order and number of days of infections (0–<6 years), but no interactions were found.

DISCUSSION

Overall, we found little evidence for an association between early-life social contacts and CABT risk. There was no evidence of an exposure–response effect of higher CABT risk for cumulative childhours of attending daycare facilities. In all, confidence intervals for all social contact measures were relatively wide and no systematic patterns were observed. However, we found some evidence for an association between number of sick days due to

Table 1. Characteristics of cases and controls

	Cases (%)	Controls (%)	Total (%)
No. of eligible cases and controls	423	909	1332
Reasons for not participating			
Refusals	18 (25)	172 (65)	190 (57)
No contact could be established	5 (7)	70 (27)	75 (22)
No approval from treating physician to contact case family	19 (27)	—	19 (6)
Time shortage – study stopped before consent was received (mainly Norway)	14 (20)	—	14 (4)
Other reasons	15 (21)	21 (8)	36 (11)
No. of participants	352	646	998
Gender			
Boys	190 (54)	353 (55)	543 (54)
Girls	162 (46)	293 (45)	455 (46)
Age group (at reference date)			
7–9	88 (25)	167 (26)	255 (26)
10–14	144 (41)	265 (41)	409 (41)
15–19	120 (34)	214 (33)	334 (33)
SES educational level of parents			
Basic	20 (6)	26 (4)	46 (5)
Medium	188 (53)	336 (52)	524 (53)
High	144 (41)	279 (43)	423 (42)
Not living with parents	—	2 (½)	—
Missing	—	3 (½)	—
Type of tumour (ICCC groups)			
Gliomas			
Astrocytomas (IIIb)	162 (46)	—	—
Other gliomas (IIIc)	30 (9)	—	—
Intracranial embryonal CNS tumours/PNET (IIIc)	62 (18)	—	—
Other			
Ependymoma (IIIa)	21 (6)	—	—
Other specified intracranial neoplasms (IIIe)	53 (15)	—	—
Unspecified intracranial neoplasms (IIIf)	24 (7)	—	—
Abbreviations: CNS = central nervous system; PNET = primitive neuroectodermal tumour; ICCC = International Classification of Childhood Cancer; SES = socioeconomic status.			

infectious disease and CABT risk. When subdividing by tumour type, the effect was restricted to glioma and embryonal CNS tumours, with the results showing statistically significant positive associations for sick days at all ages.

Our findings of no increased CABT risk in relation to social contacts are broadly consistent with earlier studies, which showed only small or no associations (Shaw *et al*, 2006; Harding *et al*, 2009; Schmidt *et al*, 2010). The overall association of CABT with sick days because of infections found in this study is in agreement with some other studies; however, the majority of studies did not find an association (Little, 1999) and, in addition, no specific infectious agent had been identified (Schüz and Kaatsch, 2002).

The observed association between CABT and infections could result from a common underlying cause, for example, an immunological factor that increases both risk of tumour

Table 2. Associations of attending daycare within 1st and 6 years of life, total daycare childhours within 6 years of life, living with other children, birth order and attending baby groups within 1st year and CABT

	Overall CABT						Glioma						Embryonal CNS tumour						Other CABT						
	Cases		Controls		OR		95% CI		Cases		Controls		OR		95% CI		Cases		Controls		OR		95% CI		
Daycare within 1st year of life																									
No	258	476	1.00	Reference	142	254	1.00	Reference	44	86	1.00	Reference	72	136	1.00	Reference	26	41	1.00	Reference	136	41	1.00	Reference	
Yes	94	167	1.11	0.80–1.55	50	93	1.02	0.65–1.60	18	33	1.17	0.54–2.53	26	41	1.28	0.68–2.40									
Attending daycare between 0 and 6 years																									
No	44	87	1.00	Reference	24	48	1.00	Reference	7	13	1.00	Reference	13	26	1.00	Reference	13	26	1.00	Reference	26	151	1.00	Reference	
Yes	308	556	0.97	0.63–1.49	168	299	0.96	0.53–1.73	55	106	1.05	0.36–3.05	85	151	0.94	0.43–2.03									
Total daycare childhours (quintiles)																									
1st Quintile	61	131	1.00	Reference	30	73	1.00	Reference	9	19	1.00	Reference	22	39	1.00	Reference	22	39	1.00	Reference	39	106	1.00	Reference	
2nd Quintile	70	107	1.36	0.87–2.11	32	60	1.39	0.75–2.59	13	24	1.22	0.40–3.75	25	23	1.62	0.72–3.65									
3rd Quintile	62	119	1.05	0.62–1.76	33	66	1.39	0.65–2.97	13	16	2.71	0.60–12.32	16	37	0.61	0.25–1.48									
4th Quintile	80	104	1.63	0.96–2.78	49	48	3.39	1.54–7.46	16	21	2.08	0.49–8.72	15	35	0.61	0.24–1.52									
5th Quintile	53	126	0.89	0.52–1.54	29	62	1.52	0.68–3.39	5	26	0.42	0.09–1.91	19	38	0.64	0.26–1.57									
Per 50 000 childhours			0.94	0.79–1.12			1.19	0.92–1.54			0.67	0.42–1.06			0.80	0.59–1.08									
Living with other children before age 6 years																									
No	15	37	1.00	Reference	9	25	1.00	Reference	2	6	1.00	Reference	4	6	1.00	Reference	4	6	1.00	Reference	6	172	1.00	Reference	
Yes	335	601	1.38	0.73–2.59	182	319	1.64	0.73–3.67	59	110	1.58	0.29–8.58	94	172	0.78	0.22–2.78									
Birth order																									
1st Born	144	249	1.00	Reference	79	134	1.00	Reference	31	46	1.00	Reference	34	69	1.00	Reference	34	69	1.00	Reference	69	106	1.00	Reference	
> 1st Born	207	391	0.89	0.68–1.16	113	212	0.90	0.63–1.29	31	73	0.63	0.34–1.16	63	106	1.14	0.67–1.95									
Attending baby groups within 1st year																									
No	90	182	1.00	Reference	46	107	1.00	Reference	19	37	1.00	Reference	25	38	1.00	Reference	25	38	1.00	Reference	38	136	1.00	Reference	
Yes	261	455	1.12	0.82–1.54	146	237	1.47	0.95–2.28	43	82	1.00	0.47–2.13	72	136	0.74	0.42–1.32									

Abbreviations: CABT = childhood and adolescent brain tumour; CI = confidence intervals; CNS = central nervous system; OR = odds ratio. Conditional logistic regression analyses, which adjusts for matching factors (age, gender and region) expressed as OR values with 95% CIs.

Table 3. Self reported sick days from infectious disease and risk of CABT

	Overall CABT				Gliomas				Embryonal CNS tumour				Other CABT			
	Cases	Controls	OR	95% CI	Cases	Controls	OR	95% CI	Cases	Controls	OR	95% CI	Cases	Controls	OR	95% CI
No. of days of infectious disease (0–<1 year)																
Once or less per month	244	440	1.00	Reference	131	245	1.00	Reference	37	73	1.00	Reference	76	122	1.00	Reference
2–3 Days per month	67	122	1.02	0.72–1.43	35	62	1.13	0.69–1.82	16	27	1.16	0.57–2.39	16	33	0.79	0.41–1.52
4 Days or more per month	32	39	1.60	0.96–2.65	23	21	2.37	1.22–4.63	5	6	1.75	0.52–5.88	4	12	0.53	0.16–1.74
No. of days of infectious disease (1–<3 years)																
Once or less per month	214	418	1.00	Reference	111	235	1.00	Reference	35	68	1.00	Reference	68	115	1.00	Reference
2–3 Days per month	81	131	1.23	0.88–1.72	45	68	1.41	0.88–2.26	15	33	0.91	0.43–1.95	21	30	1.24	0.67–2.28
4 Days or more per month	49	61	1.60	1.07–2.40	32	29	2.43	1.39–4.24	10	10	1.90	0.75–4.82	7	22	0.56	0.23–1.37
No. of days of infectious disease (3–<6 years)																
Once or less per month	237	429	1.00	Reference	126	242	1.00	Reference	36	70	1.00	Reference	75	117	1.00	Reference
2–3 Days per month	72	144	0.93	0.66–1.32	39	77	1.03	0.65–1.65	17	34	1.06	0.46–2.45	16	33	0.76	0.39–1.49
4 Days or more per month	37	43	1.62	1.00–2.63	25	18	2.87	1.45–5.67	7	7	2.08	0.64–6.70	5	18	0.43	0.15–1.25
No. of days of infectious disease (0–<6 years)																
Once or less per month	227	436	1.00	Reference	118	245	1.00	Reference	34	77	1.00	Reference	75	114	1.00	Reference
2–3 Days per month	71	117	1.27	0.89–1.80	40	59	1.60	0.97–2.62	15	23	1.48	0.68–3.22	16	35	0.75	0.38–1.49
4 Days or more per month	43	44	1.87	1.19–2.97	29	22	2.93	1.57–5.50	9	5	4.21	1.24–14.30	5	17	0.42	0.15–1.78

Abbreviations: CABT = childhood and adolescent brain tumour; CI = confidence intervals; CNS = central nervous system; OR = odds ratio. Conditional logistic regression analyses, which adjusts for matching factors (age, gender and region) expressed as OR values and with 95% CI.

development and susceptibility to infectious disease. Also, we cannot rule out that inverse causality could be an explanation, as having a yet undiagnosed brain tumour could make the case children more susceptible to infections. Both of these explanations would fit with the fact that we observed no clear association with particular age periods when the infections occurred.

We estimated infections in the first 6 years of life from self-report (infectious calendar developed for the purpose of this study, see Supplementary Appendix 1 online). Accurate recall of infectious episodes is, however, demanding (Schmidt *et al*, 2010) and laypersons may have difficulty in separating sick days due to infection from sick days for other reasons. Furthermore, case parents may have over-reported exposure, in an attempt to provide an explanation for the disease of their child; if so, one might expect them to do this for all age periods in the questionnaire, but inspection of the data for the most sick children showed no clear evidence of such an effect (data not shown). Alternatively, one

could speculate that case parents might under-report sick days, as infections may be trivial compared with the later burden of having a child with a cancer diagnosis. In addition, common early symptoms of CABT include headache, nausea and vomiting (Wilne *et al*, 2007), and there may be a diagnostic delay of several years (ng-Tan and Franco, 2007, 2008; Wilne *et al*, 2007; Raab and Gartner, 2009) before the child is diagnosed with CABT; therefore, it is possible some reported infections of cases could reflect prodromal symptoms, even though we excluded any exposure occurring within 2 years of diagnosis. Altogether, the above factors may have introduced differential information bias. In this case we would, however, expect to find the same effect for all subtypes of CABT, whereas we only saw elevated risk estimates for glioma and embryonal CNS tumours, suggesting that biased reporting of infectious diseases is not a major concern. On the other hand, the group of other CABTs is small and the difference may be due to random variation.

Another concern is if first born children may have had more sick days due to more concerned first time parents or due to better recollection of early life events (Sou *et al*, 2006). There was, however, no evidence of differential reporting of sick days for the first born children in our data as there was no statistically significant interaction between birth order and number of sick days.

Regarding social contacts, the above-mentioned diagnostic delay (Raaschou-Nielsen *et al*, 2006; ng-Tan and Franco, 2007, 2008; Wilne *et al*, 2007; Raab and Gartner, 2009) suggests confounding by indication as a potential concern as cases may have attended daycare less often compared with controls because of prodromal symptoms or other factors relating to a latent and undiagnosed CABT. This would lead to an underestimation of the association between social contacts and the risk of CABT.

Strengths of this study include the high participation rate, reducing the potential of selection bias, and the use of nationwide and high-quality registries (Tulinius *et al*, 1992; Storm *et al*, 1997; Barlow *et al*, 2009) in addition to case validation from treating physicians in hospitals ensuring a complete case ascertainment. Furthermore, cases were validated by unequivocal diagnostic imaging or histological confirmation ensuring correct diagnoses of included cases. The complete Scandinavian and Swiss population registers provided an optimal sampling frame for population-based controls.

Daycare attendance before the age of 6 years was high in all countries (range: 63–97%), making it a substantial source of social contacts with other children and therefore also for repeated contact with infectious agents. This in combination with a range of other measures of social contacts and infectious diseases allowed us to establish a quite detailed picture of the children's total exposure. This included also social contacts at home, where we could account for the complex modern family structure with cohabiting full, half- and step-siblings, whereas previous studies have not had any such information or at best had registered maternal birth order (Emerson *et al*, 1991; Linet *et al*, 1996; Heuch *et al*, 1998; Mogren *et al*, 2003; Von Behren and Reynolds, 2003; Altieri *et al*, 2006; Shaw *et al*, 2006; Schmidt *et al*, 2010).

With such a generally high proportion of children attending daycare, it became difficult to investigate daycare as a risk factor; however, we created the score of childhours at daycare as exposure gradient and did not observe an association with CABT risk when comparing children of the highest and lowest quintile of childhours at daycare. The distribution of attending daycare was skewed between the countries; we did, however, not have sufficient statistical power to perform country-specific analyses, but sensitivity analysis, removing one country at a time, did not substantially alter the results (data not shown).

Whereas interview information about birth order and living with other children is expected to be accurate, information on daycare attendance may be difficult to recollect many years later. We believe, in contrast to the reported infectious diseases, that it is unlikely that case and control parents remember daycare attendance differently. There is, however, the possibility that non-differential bias could influence the risk estimates, possibly leading to a dilution of the risk.

In conclusion, this study provides little evidence of an association between increased social contacts in early life, as measured by daycare attendance, participation in baby groups or living together with other children, and the risk of CABT in 7–19 year olds. However, we observed more frequent reported sick days because of infections in the first 6 years of life associated with the risk of glioma and possibly embryonal brain tumour. Although the association could result from chance or recall bias, it needs to be further studied to identify whether infectious disease early in life could represent early symptoms of CABT, have the same underlying cause as CABT or modulate the risk of developing a CABT.

ACKNOWLEDGEMENTS

The Danish part of the CEFALO study was supported by the Danish Strategic Research Council (Grant numbers 2103-05-0006 and 2064-04-0010). This particular part on social contacts and infections was funded by the Danish Childhood Cancer Foundation. The Swedish CEFALO study was supported by grants from the Swedish Council for Working Life and Social Research (Grant numbers 2004-0504 and 2007-0224), the Swedish Research Council (K2008-70X-15366-04-3), the Swedish Cancer Society (09 0666), the Swedish Childhood Cancer Foundation (Grant numbers PROJ06/050 and PROJ09/086) and the Swedish Radiation Protection Authority (SSI P 1572). The Swiss part of the CEFALO study was supported by the Swiss Federal Office of Public Health (Grant number 05.001626), the Swiss Research Foundation on Mobile Communication (Grant number A2006.18) and the Swiss National Science Foundation (Grant number PDFMP3_122873). The Norwegian CEFALO study was supported by the Research Council of Norway (Grant number 175163/V40).

Sweden: The Swedish collaborative group thanks the hospital staff, the Swedish Regional Cancer Registries and the Swedish Childhood CNS Tumour Group for their collaboration and valuable contributions to the CEFALO study. We thank the following key persons at the hospitals: Dr Johan Lundgren (Department of Pediatrics, University Hospital, University of Lund); Dr Ulf Samuelsson (Department of Pediatrics, University Hospital, Linköping); Dr Stefan Holm (Department of Pediatrics, Astrid Lindgren Children's Hospital, Karolinska University Hospital, Stockholm); Dr Per Erik Sandström (Department of Pediatrics, University Hospital, Umeå); Dr Bo Strömberg (Department of Pediatrics, Akademiska Children's Hospital, Uppsala). The Swedish Childhood Cancer Registry was a valuable resource for the clinics. We gratefully acknowledge the research nurses Birgitta Ohlander and Annika Lilienberg for skilful work.

Switzerland: The Swiss collaborative group would like to thank Daniela Jenni, Diane Rey and Nicole Jakubowitz, who conducted interviews with participants. We would also thank the following persons from the hospitals and cancer registries for their valuable collaboration: Karin Zimmermann and Nadine Beusch (Department of Pediatric Haematology and Oncology, Inselspital Bern), Ursula Schönenberger (Secretariat Neurosurgery, Canton Hospital of Aarau), Verena Stahel (Department Haematology and Oncology, Children's Hospital Basel), Nicole Jakubowitz, Sandra Ettl (Children's Hospital Lucerne), Maria Isabel Bartolome-Vegas (Secretariat, Cantons Hospital Lucerne), Nadja Blöchliger (Secretariat, University Hospital Zürich), Dr Luisa Nobile (Department of Pediatrics, Canton Hospital Ticino), Franziska Hochreutener (Secretariat, Children's Hospital St Gallen), Heike Markievicz (Department of Oncology, Children's Hospital Zürich), Rosemarie Burri (Secretariat Neurosurgery, Insel Hospital Berne), Professor Dr Hans Landolt (Department Neurosurgery, Canton Hospital Aarau), Karl Kothbauer (Department Neurosurgery, Canton Hospital Lucerne), Regula Angst (Department Oncology, Canton Hospital Aarau), Professor Dr Michael Paulussen (Department Pediatric Oncology and Haematology, Children's Hospital Basel), Dr Heidi Baechli (Department Neurosurgery, University Hospital Basel), Professor Andreas Hirt (Department Pediatric Haematology/Oncology, Insel Hospital Bern), Anton Lukes (Department Pediatric Neurosurgery, University Hospital Bern), Ueli Cafilich (Children's Hospital Lucerne), Heinz Hengartner (Department Oncology and Haematology, Children's Hospital St Gallen), Bettina Gers (Department Neurosurgery, Canton Hospital St Gallen) and René Bernays (Department Neurosurgery, University Hospital Zürich).

Norway: The Norwegian collaborative group would like to thank Dr Med Finn Wesenberg (Pediatric Department, Rikshospitalet

University Hospital, Oslo), who contributed to the planning of the project and verified the Norwegian case patients. We also thank some other key persons at the hospitals: Dr Rupavathana Mahesparan (Neurosurgical Department, Haukeland University Hospital, Bergen), Dr Mikael Donner (Pediatrics Department, Haukeland University Hospital, Bergen), Dr Randi Nygaard (Department of Pediatrics, St Olav University Hospital of Trondheim) and Dr Johan Cappelen (Department of Neurosurgery, St Olav University Hospital of Trondheim). We gratefully acknowledge research assistant Margareth Kaurin for her skilful work.

Denmark: The Danish collaborative group is thankful for all the help and cooperation from Danish hospitals. We would especially like to express our gratitude to the following: Staff specialist Astrid Sehested (Copenhagen University Hospital), Consultant neurosurgeon Lars Bøgeskov (Department of Neurosurgery, Copenhagen University Hospital), Consultant neurosurgeon Jannick Brennum (Department of Neurosurgery, Glostrup Hospital), Clinical associate professor Niels Carlsen (Department of Paediatrics, Odense University Hospital), Consultant neurosurgeon Morten Søb (Department of Neurosurgery, Odense University Hospital), Consultant paediatrician Steen Rosthøj (Department of Paediatrics, Aarhus University Hospital, Aalborg Hospital), Chief neurosurgeon Preben Sørensen (Department of Neurosurgery, Aarhus University Hospital, Aalborg Hospital), Consultant neurosurgeon Leif Christensen (Department of Neurosurgery, Aarhus University Hospital, Aarhus Hospital), Consultant paediatrician Niels Clausen (Department of Paediatrics, Aarhus University Hospital Skejby), Consultant paediatrician Henrik Schrøder (Department of Paediatrics, Aarhus University Hospital Skejby).

We thank Drs Jorgen H Olsen and Christoffer Johansen for their support in receiving the initial funding for the CEFALO study in Denmark. Furthermore, we would also like to thank Pernille Clausen, Henrik Gregersen, Martin Gregersen, Daniel Kristoffersen and Kenneth Widén at the Danish Cancer Institute for technical support. Also, a special thanks to Lissa Churchward and Gro Munk Nielsen at the Danish Cancer Society for supporting the administrative work.

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Supplementary Information accompanies this paper on British Journal of Cancer website (<http://www.nature.com/bjc>)