Obstetric Events as a Risk Factor for Febrile Seizures: A Community-Based Twin Study

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Adverse events during the perinatal period have traditionally been thought to contribute to the risk of febrile seizures although an association has not been found in large epidemiological studies. Disease-discordant twins provide a means to assess the role of non-shared environmental factors while matching for confounding factors and avoiding difficulties of epidemiological studies in singletons. This study aimed to examine the association of obstetric events and febrile seizures in a community-based twin study. Twenty-one twin pairs discordant for febrile seizures were ascertained from a community-based twin register. Obstetric events were scored using the McNeil-Sjöström Scale for Obstetric Complications and expressed as a summary score (OC score). The frequency of individual obstetric events in affected and unaffected twins, the within-pair differences in OC scores and other markers of perinatal risk including birthweight, birth order and Apgar scores were examined. No significant difference was found in the frequency of individual obstetric events, nor in OC scores between affected and unaffected twins. No differences in birth weight, birth order, 1- or 5-minute Apgar scores were observed. Our results confirm previous findings that obstetric events are not associated with the risk of febrile seizures.

Keywords: epilepsy, seizures, birth trauma

Febrile seizures are the most common neurological problem in children and affect between 2% and 5% of children in the first 5 years of life (Nelson & Ellenberg, 1976). Twin and family studies have repeatedly demonstrated the importance of genetic factors in the etiology of the condition (Kjeldsen et al., 2002; Offringa et al., 1994; Tsuboi, 1987). Nevertheless, a significant proportion of the tendency to develop febrile seizures appears to be nongenetic, suggesting unknown environmental factors.

Obstetric events occur at the most vulnerable time in human life and major acquired brain lesions during pregnancy and delivery, such as perinatal hemorrhage, are a well-recognized cause of symptomatic seizure disorders (Hauser et al., 1993). Hence, it is commonly assumed that less grave events might be risk factors for less severe seizure disorders such as Febrile Seizures.

Indeed, results from early studies suggest that obstetric events are more common in children with febrile seizures than in controls (Heijbel et al., 1980; Millichap, 1968; Tsuboi, 1986). However, large population-based studies have not supported the hypothesis that events during pregnancy, labor-delivery or the neonatal period have a large contribution to the risk of developing febrile seizures (Greenwood et al., 1998; Nelson & Ellenberg, 1990; Verity et al., 1985). Nevertheless, individual events, including maternal smoking (Vestergaard et al., 2005), shorter gestation (Vestergaard et al., 2003) and bleeding during pregnancy (Greenwood et al., 1998), have been found to be associated with febrile seizures. These associations were mostly weak.

Epidemiological studies investigating the association of obstetric events with febrile seizures face several difficulties, including ascertainment, selection of cases and controls and statistical power (Deymeer & Leviton, 1985). Furthermore, sensitive measurement instruments for obstetric factors are often not used, and it is impractical to implement detailed clinical analysis and phenotyping in large epidemiological studies.

Disease discordant twin pairs minimize many of the difficulties in studies of singletons, and control for known and unknown confounding factors. For example, maternal factors such as age at birth and the intrauterine environment are shared equally by the discordant twins and do not disturb the interpretation of associations with obstetric factors unique to each twin. While studies in disease-discordant twins are unable to assess the role of shared factors during pregnancy, these studies are particularly sensitive to nonshared events during labor, delivery and the neonatal period. Hence, studies in disease-discordant twins provide a unique measure to complement epidemiological studies in singletons.

Scoring and rating of obstetric events is challenging and detailed. Therefore, standardized scoring systems

such as the McNeil-Sjöström Scale have been developed (McNeil & Sjöström, 1994; McNeil et al., 1994a;). The McNeil-Sjöström Scale scores and rates complications and conditions occurring during the pregnancy, labor-delivery and neonatal periods. The severity weightings of this scale are thought to reflect the known or inferred harm to the offspring with special focus on the offspring's central nervous system. The high sensitivity and comprehensiveness of this scale has been demonstrated in studies of schizophrenia (McNeil, 1995; McNeil et al., 1994a; McNeil et al., 2000).

In the present study, we applied the McNeil-Sjöström Scale in a matched twin-pair design based on twins discordant for febrile seizures. Our aim was to combine the power of the twin design with a sensitive measuring instrument in order to investigate the association of obstetric factors with febrile seizures in a community-based cohort.

Methods

Twin Sample and Ascertainment

Twins were ascertained through the Australian Twin Registry, a volunteer community-based register (Berkovic et al., 1993; Berkovic et al., 1998; Hopper, 2002). Twins aged between 1 and 18 years, born in the period 1980 to 1996, with both twins living in Victoria, were targeted to ensure that medical records of their birth and early seizure history could be obtained. A seizure-screening questionnaire was mailed to the parents of twin pairs. A second mailing was sent to those who failed to respond. When parents responded affirmatively to questions about a history of febrile convulsions, seizures or epilepsy in one or both twins, they were contacted by phone and both twins were invited to participate further in the study. Written informed consent was obtained from the study participants or their parents if the twins were under 18 years of age. This study was approved by the Ethics Committees of Austin Health and the Australian Twin Registry, University of Melbourne.

Clinical Evaluation

A comprehensive epilepsy assessment of each twin was obtained using a structured interview and validated questionnaire (Reutens et al., 1992), clinical evaluation by an experienced epileptologist (SFB) and review of relevant clinical investigations. Both twins underwent EEG recordings and a neurological and general examination. Previous clinical records and reports of relevant investigations were obtained if available. Diagnoses of epileptic syndromes, including Febrile Seizures, were made in accordance with the classification of the International League Against Epilepsy (1989). Twins with an epileptiform abnormality on EEG but no history of seizures were regarded as unaffected. For same-sex twin pairs, a blood sample was obtained for zygosity testing using polymorphic microsatellite markers. False positives were those

twins reporting seizures in whom subsequent evaluation excluded epileptic seizures (e.g., syncope).

Documentation of Obstetric Events

Information about pregnancy, birth and early developmental history for each twin was obtained from the mother, and the twins themselves where appropriate, using a structured questionnaire. Birth records were obtained from as many independent sources as possible including the hospital of birth, the obstetrician involved and the attending pediatrician. The McNeil-Sjöström Scale was applied to these data. Apgar scores for 1 and 5 minutes were obtained from medical records. The Apgar scores were analyzed separately to facilitate comparison with data from previous epidemiological studies (Sun et al., 2006).

McNeil-Sjöström Scale for Obstetric Complications

The McNeil-Sjöström Scale for Obstetric Complications uses a severity weighting system that reflects the inferred probability of harm to the offspring with special focus on the offspring's central nervous system (McNeil et al., 1994b). The scale contains many hundreds of events including obstetric events, treatments and conditions that are considered potentially harmful to the offspring and can accommodate information obtained from a variety of qualitatively different sources.

The severity ratings in the McNeil-Sjöström Scale range from 1 to 6 (McNeil & Sjöström, 1994; McNeil et al., 1994a). Severity levels 1 to 3 (e.g. amniocentesis is designated as a level 3) are designated 'not harmful or relevant' to 'potentially, but not clearly harmful or relevant'. Level 4 (e.g., breech presentation) is regarded as 'potentially clearly harmful or relevant', whereas level 6 (e.g., intracerebral hemorrhage), may result in 'very great harm to or deviation in offspring'.

The McNeil-Sjöström Scale is an ordinal rather than interval scale. A summary score can be used, such as the number of different obstetric events at or above a given level of severity. A summary score for 'severe obstetric complications', used in previous applications of the McNeil-Sjöström Scale (McNeil et al., 1994a; McNeil et al., 1994b; McNeil et al., 2000), summates the number of events in pregnancy with a score of greater than or equal to 3 and events in the labor–delivery and neonatal period with a score of greater than or equal to 4. This summary score for all three reproductive periods is referred to as the OC score.

Statistical Analysis

Odds ratios for febrile seizures associated with individual obstetric complications (considered as dichotomous variables consistent with the contribution of each to the OC score) were calculated with Woolf's method for independent proportions (Woolf, 1955). Within-twin pair differences in OC scores (ΔOC), birthweights and 1- and 5-minute Apgar scores were tested using the McNemar test, Wilcoxon rank sum tests or paired t tests, as appropriate; all reported p values are two-sided. We tested whether

Demographic Characteristics of Twin Pairs Discordant For FS

	Affected twin	Unaffected twin
Total	21	
Male	15	9
Female	6	12
Zygosity		
Monozygotic (MZ)	4 *	
Dizygotic (DZ)	17 †	
Gestational age at delivery in weeks		
Mean ± SEM	36.5 ± 0.5	
Maternal age in years		
Mean ± SEM	30.2 ± 0.8	

Note: * 2 male pairs, 2 female pairs
† 5 male pairs, 2 female pairs, 10 male/female pairs
SEM, standard error of the mean

individual obstetric events were associated with each of recurrence and age of onset among affected twins using Pearson's Chi squared test corrected for multiple testing using Bonferroni's method. For this analysis age of onset was dichotomized at the median with subjects with values less than the median designated 'early onset'. Associations between ΔOC and each of recurrence and age of onset were assessed via a two-sample t test and regression analysis, respectively. Age of onset was also considered as a dichotomous variable (see above) and the association with ΔOC was assessed via a two-sample t test. Posthoc power calculations were carried out using Minitab.

Results

Ascertainment and Demographics

The validated seizure-screening questionnaire was mailed to 2554 twin pairs. A total of 1919 pairs completed and returned the questionnaires (75% response rate) of whom 204 (10.6%) reported a history of febrile convulsions, epilepsy or suspected seizures in one or both twins. Of these, 83 pairs refused to participate further due to logistical difficulties with time or travel or lack of interest.

Of the remaining 121 pairs, 68/121 twin pairs were excluded as they were false positives (30/68), were concordant for seizures (20/68) or adequate obstetric data could not be obtained (18/68), leaving 53 twin pairs for the analysis.

Seizures with fever were reported in 29/53 pairs, of which 21 twin pairs were discordant for the classical Febrile Seizure syndrome; eight were excluded due to additional seizure types, because seizures with fever occurred outside the age range of six months to six years or were in association with other neurological symptoms or lesions.

The mean age (± standard error) of subjects at the time of recruitment was 3.8 ± 0.5 years and the average

age at seizure onset in the affected twin was 1.8 ± 0.1 years with a follow-up of 9.4 ± 0.5 years after the affected twin developed seizures. Demographic details of the twin sample are displayed in Table 1. Of the 21 affected twins, 15/21 had simple febrile seizures, 4/21 had complex febrile seizures and 2/21 twins had febrile status. Recurrent febrile seizures occurred in 7/21 affected twins (3/7 had two febrile seizures and 4/7 had between three and six febrile seizures); 14/21 of the affected twins had just a single episode.

Quality of Obstetric Data

In all 21 twin pairs, a retrospective report was obtained from the mother. In 20/21 twin pairs, this information was substantiated by hospital records; one twin pair with detailed maternal historical data only was also included. In 19/21 twins, three or more independent source records were obtained.

Obstetric Events and the OC Score

Common obstetric events above the severity threshold and occurring at least in three twin pairs are listed in Table 2, the OC scores are shown in Table 3. There was no evidence of differences in the frequency of individual obstetric events (all $p \geq .15$), nor in OC scores ($p = .49$) between affected and unaffected twins. In 7/21 twin pairs, the affected twin had a higher OC score, while in 12/21 twin pairs, a higher OC score was found in the unaffected twin ($p = .25$; Table 4). The 95% confidence interval for the mean ΔOC excluded +1 suggesting that mean OC scores are not higher in affected compared to unaffected twins.

The mean ΔOC was −0.3 ± 0.5 (Table 3), with values ranging between −4 and +3 across the 21 twin pairs (see Figure 1). In 12/21 twin pairs, the within-pair difference was equal or less than a single OC score. A secondary analysis of ΔOC for each of the three reproductive periods separately showed no evi-
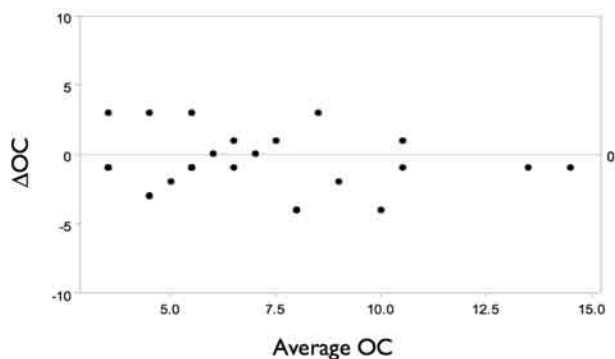

Figure 1

Differences in the summary score for severe obstetric complications (OC score) in twin pairs discordant for febrile seizures. Intra-pair differences between the summary scores for severe obstetric complications (ΔOC) are plotted against the average summary score per twin pair ($n = 21$, two twin pairs have an average OC of 3.5 and ΔOC of −1). ΔOC is the OC score of the affected minus the OC score of the unaffected twin, that is, ΔOC is positive if the affected twin has more obstetric events than the co-twin.

Table 2

Most Common Obstetric Events in the Twin Sample with Febrile Seizures (n = 21)*

Obstetric complication	Affected twin only	Unaffected twin only	Both twins	Severity score[†]	Odds ratio (95% CI)[‡]
Pregnancy					
Weight disadvantage	9	6		*4, 5*	**1.88** (0.52–6.76)
Bleeding during pregnancy			10	*3, 4, 5*	
Maternal smoking			6	*3, 4, 5*	
Pulmonary embolism			4	*4, 5*	
Maternal hypertension			5	*3, 4*	
Maternal drugs, clomiphene			4	*5*	
Small for gestational age	1	0	1	*4*	**2.11** (0.18–25.17)
Maternal morning sickness			3	*3, 4, 5*	
Labor-Delivery					
Breech presentation	6	4	1	*4*	**1.60** (0.41–6.19)
Forceps	2	2	3	*4, 5*	**1.00** (0.24–4.14)
C-section, emergency			7	*5*	
General anaesthesia			4	*4*	
Breech, assisted	2	2		*4*	**1.00** (0.13–7.85)
Fetal distress	2	1		*4*	**2.11** (0.18–25.17)
Neonatal					
Low Apgar 1 min	5	4	4	*4, 5*	**1.22** (0.36–4.19)
Prematurity			7	*4, 5, 6*	
Onset breathing > 1 min	1	3	3	*4*	**0.58** (0.14–2.49)
Phototherapy	1	1	6	*4*	**1.00** (0.28–2.49)
Small for gestational age	3	3		*4*	**1.00** (0.18–5.63)
Hypothermia	0	1	2	*4*	**0.48** (0.04–5.68)
Birthweight < 2500g	3	0	1	*4*	**4.71** (0.48–46.23)

Note: * Obstetric events listed were found in at least two twin pairs and have a severity score ≥ 3 for pregnancy and ≥ 4 for the labor-delivery and neonatal periods. Scores for 'twin birth' have been omitted from this list.

[†] 'Severity score' relates to the score for the individual event given by the McNeil-Sjöström scale, individual events can be coded with different severity scores.

[‡] Odds ratios were calculated using Woolf's method for independent proportions and determined for events that could be unequally shared between twins.

dence of differences from zero for the pregnancy (mean = 0.1 ± 0.1), labor-delivery (mean = −0.2 ± 0.3) and neonatal period (mean = −0.1 ± 0.3). Subscores for pregnancy were identical in all but one twin pair, for which an additional prenatal event was scored in the affected twin.

Other Markers of Perinatal Risk

Birthweight, birth order and Apgar scores did not differ between affected and unaffected twins (all $p ≥ .28$, Table 3). Apgar scores for 1-minute and 5-minutes were available for 19 twin pairs (Table 4). In 6/19 and 3/19 twin pairs, the affected twin had a worse (lower) Apgar score than the unaffected, compared with 8/19 and 2/19 in the opposite direction.

Associations of Obstetric Events and the OC Score with Clinical Parameters

No single obstetric event was significantly more frequent in affected compared to unaffected twins (all $p ≥ .15$). No single event was associated with recurrence ($p ≥ .28$). Twin pairs with recurrent seizures had a nonsignificantly higher mean ΔOC than twin pairs with single seizures (0.71 vs. −0.87, $p = .16$). The age of seizure onset showed a weak negative correlation with ΔOC (regression analysis $p = .04$; t test $p = .03$). There was no difference in ΔOC between twin pairs with simple febrile seizures compared to twin pairs with complex febrile seizures or febrile status ($p = 1$).

Post-Hoc Power Calculation for Obstetric Complications and Apgar Scores

The present study had more than 80% power at the 0.05 level of significance (two-sided) to detect a mean within-pair difference of 1.4 obstetric complications or more. For differences in Apgar scores, the present study had more than 80% power to detect a mean within-pair difference of 1.5 or more in 1-minute Apgar scores, and of 0.6 or more in 5-minute Apgar scores.

Discussion

We have investigated the association between obstetric events and Febrile Seizures using a disease-discordant twin pair design by comparing several markers of perinatal risk and by applying the McNeil-Sjöström Scale for obstetric complications. The disease-discordant twin pair design has many attractive qualities and can produce compelling results using smaller sample sizes compared to studies of singletons alone. Variance can be reduced, as the known and unknown confounding factors shared within pairs are controlled for by design. Smaller samples make it practical to perform detailed clinical analysis of seizure syndromes and assessment of obstetric events using comprehensive scales.

In the present study, the summary score for obstetric complications (OC score), 1-minute and 5-minute Apgar scores, birthweight and birth order did not differ within twin pairs discordant for febrile seizures.

Table 3

Markers of Perinatal Risk in the Twin Sample with Febrile Seizures

	Affected twin	Unaffected twin	Difference within pairs[*]	95% CI (difference)	p value (difference)
Obstetric Complication (OC) score					
Mean[†] ± SEM (n = 21)	7.1 ± 0.7	7.5 ± 0.8	−0.3 ± 0.5	(−1.3, 0.6)	0.49
Median[‡]	7	7	−0.5	(−1.5, 1)	0.47
Birth weight in grams					
Mean[†] ± SEM (n = 21)	2506 ± 114	2546 ± 105	−40 ± 110	(−269, 196)	0.72
Birth Order					
First born (ratio)[§]	13/21 (0.62)	8/21 (0.38)			0.38
1 minute Apgar score					
Mean[†] ± SEM (n = 19)	7.3 ± 0.4	6.8 ± 0.5	0.6 ± 0.5	(−0.5, 1.7)	0.28
Median[‡]	7	7	0.5	(−0.5, 1.5)	0.38
5 minute Apgar score					
Mean[†] ± SEM (n = 19)	9.4 ± 0.2	9.4 ± 0.2	0 ± 0.2	(−0.5, 0.5)	1
Median[‡]	10	10	0	(−0.5, 0.0)	1

Note: [*] Affected minus unaffected
[†] p-value and 95% CI calculated using the paired t-test
[‡] p-value and 95% CI calculated using the Wilcoxon rank sum test
[§] One sample test for the proportion of affected twins that were first born against a null hypothesis that the proportion is 0.5
SEM: Standard error of the mean

Table 4

Within-Pair Comparison of Obstetric Complications (OC) and Apgar Scores

	Affected worse than Unaffected[*]	Affected same as Unaffected	Affected better than Unaffected	Proportion of affected worse (95% CI)[†]	p value[‡]
Obstetric Complication (OC) score					
n = 21 pairs	7	2	12	0.33 (0.14, 0.57)	0.25
1 minute Apgar score					
n = 19 pairs	6	5	8	0.31 (0.13, 0.57)	0.59
5 minute Apgar score					
n = 19 pairs	3	14	2	0.15 (0.03, 0.40)	0.65

Note: [*] 'worse' and 'better' are used, since numerical differences in Apgar scores and OC scores have opposite meanings, that is, a *lower* Apgar score is 'worse' as is a *higher* OC score
[†] Proportion of twin pairs in which the affected has a *lower* Apgar score or a *higher* OC score
[‡] McNemar's test used

Several individual obstetric events were more common in affected compared to unaffected twins. However, these differences were not statistically significant and were not reflected in the summary score. This study was sufficiently powered to detect a mean within-pair difference of 1.5 obstetric events. In addition, a mean within-pair difference of 1.5 Apgar score units for 1 minute and a single Apgar score unit for 5 minutes could be detected with a power of greater than 80%. Regarding birth order, the firstborn twin was affected more often than the second born. Although this difference was not statistically significant, the direction of the difference undermines the long-held belief that second born twins are at higher risk for disorders of the central nervous system.

In contrast to previous studies investigating the role of obstetric events in twins with Febrile Seizures (Schiottz-Christensen, 1973), our cohort was community-ascertained, followed over an average of almost 10 years, and diagnosed according to modern diagnostic criteria, excluding affected twins with later epilepsy, febrile seizures plus (Scheffer & Berkovic, 1997) and underlying neurological disorders. Hence, our twin cohort was representative and homogenous with respect to diagnosis.

Studies in discordant twins are incapable of assessing prenatal factors that are shared by both twins. Hence our study was unable to investigate the role of previously implicated shared prenatal risk factors such as maternal smoking (Vestergaard et al., 2005), bleeding during pregnancy (Greenwood et al., 1998) or shorter gestational age (Vestergaard et al., 2003). In addition, markers such as birthweight, which might indicate differences in prenatal environment, were not found to be different between affected and nonaffected twins. Consistent with this, subscores for pregnancy were identical in all but one twin pair. In conclusion, the 19 twin pairs in our study were basically matched for detectable prenatal influences including known risk factors, resulting on a focus of nonshared perinatal and postnatal factors. Given the nature of the twin design, we cannot exclude that shared obstetric complications

frequently found in our twin sample contribute to the risk of febrile seizures. However, twin birth itself including the known higher frequency of obstetric complications in twins is not a risk factor for seizure disorders (Berkovic et al., 1993).

In addition, we have investigated associations with different clinical parameters of febrile seizures, including age of onset, recurrence and seizures types (simple vs. complex febrile seizures or febrile status). Among the different associations tested, only the correlation between a positive within-pair difference in the summary score and an early age of onset was detected, warranting further replication.

Large population-based studies in Great Britain (Greenwood et al., 1998; Verity et al., 1985) and the United States (Nelson & Ellenberg, 1990) have not supported the idea that perinatal events are important risk factors for febrile seizures, even though some prenatal events might represent minor risk factors. Our study, with the power of the twin design, detailed phenotyping and exhaustive assessment of perinatal factors is a powerful and instructive confirmation of these results. Even when individuals were matched for most maternal and intrauterine factors, no association between obstetric events and the risk for febrile seizures was found.

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Disclosure of Conflicts of Interest

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