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Aetiological factors and development in subjects with obstructive sleep apnoea

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Objective: To examine whether maternal pregnancy complications, adverse birth events, respiratory illnesses, or developmental difficulty were increased in neurologically normal children with obstructive sleep apnoea (OSA) and whether severity of OSA adversely affects the child's development and temperament.
Methodology: Maternal report of perinatal events, respiratory illness and developmental difficulty in 37 children with OSA was contrasted with a comparison group (n = 67). Children with OSA were assessed developmentally (Griffiths Scales), had a parental rating of temperament (Australian Temperament Scale) and attended an overnight polysomnographic sleep study.
Results: Children with OSA had an increased prevalence of adverse maternal pregnancy and perinatal events, respiratory disease and developmental concerns. Limited associations were found between the severity of OSA and development or temperament difficulty.
Conclusions: This study suggests a relationship between OSA, though not its severity, and pre/perinatal adversity and child development. Polysomnographic and detailed developmental assessment of community-based samples of children with OSA and control children are necessary to confirm these findings.

Key words: aetiology; children; development; obstructive sleep apnoea; temperament.

Approximately 0.7% of children from 4 to 5 years of age experience breathing and sleep disturbance associated with obstructive sleep apnoea (OSA).[1] Adult studies have found that OSA and particularly related parameters such as hypoxemia and obstructive events are likely to have serious consequences for physical, cognitive and behavioural outcome.[2,3] The evidence for developmental and behavioural consequences of OSA in children, however, is limited and is based on studies which often describe case series of neurologically impaired children,[4] or which lack formal developmental testing of the children or detailed polysomnographic measures of the disease itself.[5–8] Though it lacked detailed polysomnographic data, the study of Ali *et al.*[9] reported a higher prevalence of attentional difficulties in children with sleep and breathing disorders, and an improvement following adenoidectomy. Population polysomnographic data for children and inconsistencies in definitions of disease make interpretation of any association between disease and development difficult.[10] Furthermore, there is a need to assess the association between adverse intrapartum events, perinatal events, and respiratory related illness with OSA as these may predispose the child to both breathing disorders and developmental difficulty.[11–13]

In this study we examined whether the prevalence of pregnancy complications, perinatal risk factors, respiratory illnesses or developmental difficulty were increased in neurologically normal children with OSA. We also examined whether the severity of OSA was associated with the nature or degree of disturbance in development and temperament of these children.

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SUBJECTS AND METHODS

OSA subjects

Fifty-six children less than 5 years of age were referred to the Mater Children's Respiratory Sleep Clinic during a 12-month period for assessment of OSA symptoms. All subjects were assessed clinically by a respiratory paediatrician prior to a polysomnographic sleep study which was performed within 4 weeks of the clinical visit. All children had a history of frequent snoring for at least 6 months, plus either witnessed apnoea, restlessness during sleep or daytime sleepiness.

Of these 56 children, 40 (28 male, 12 female, mean age 32.5 months, age range 2–57 months) were considered by a paediatrician to be neurologically normal and were the subjects for this study. The 16 neurologically abnormal children excluded from the study included 2 children with cerebral palsy, 3 children with meningomyelocele, 4 children with severe global delay, 1 child with microcephaly and epilepsy, 2 children with Prader–Willi Syndrome, 1 child with tuberous sclerosis and epilepsy, 1 child with Duchenne muscular dystrophy, 1 child with Crouzon's disease and 1 child with autism.

Polysomnographic study (PSG)

For the 40 neurologically normal children, the mean hours of recorded sleep time was 8.0 h (range 5.3 h to 10.4 h). Inter-scorer variability between the three observers (IBM,MAH,PDW) was less than 10%. Apnoea was defined as any cessation of air

flow as measured by chest and abdominal motion and oronasal flow that was longer than the preceding two breaths. Apnoeas were subclassified as central, obstructive and mixed. Hypopneas were defined as any amplitude reduction in air flow of 50% or greater that lasted longer than the preceding two breaths. Hypopneas were subclassified as central, obstructive or mixed. An Obstructive Event Index (OEI) was defined as the sum of obstructive apnoeas, obstructive hypopnoeas, mixed apnoeas, and mixed hypopnoeas divided by the total sleep time in minutes then multiplied by 60. Oxygen saturation data were expressed as mean data for the total study time. Awake time and artefactual/movement oxygen saturation data were deleted in accordance with previously described methods.[14] Desaturation data were expressed as the mean number, time and percentage of the total study time equal to or less than 95%, 92%, 90% and 85% saturation, respectively.

OSA definition

As described by Carroll *et al.*[15] OSA was defined according to the obstructive event OEI from the PSG study. Children were rated as primary snorers (OEI < 1, $n = 3$), or as having mild OSA (OEI ≥ 1 and < 5, $n = 21$), or moderate/severe OSA (≥ 5, $n = 16$). The OEI definition differs slightly to that of Carroll *et al.* in that no attempt was made to temporally link the oxygen desaturation to the respiratory events of apnoea and hypopnoea. The three primary snorers were excluded from the analysis.

Equipment

Monitoring equipment included an electroencephalograph (EEG: C3/A2, 02/A1; 10–20 international placement), two channels of electro-occulogram (EOG: KIC/A2, ROC/A1), chest and abdominal motion (Respitrace, Ambulatory Monitoring Inc., New York, USA), oxygen-saturation measurements (CSI: 504US P Criticare Systems, Waukesha, WI, USA), and transcutaneous carbon dioxide levels (Radiometer, Copenhagen, Denmark). Airflow as measured by pressure transducers (Differential Pressure Transducer no. 4500, Vacumetrics Inc., California, USA) and thermistors was recorded continuously onto a computerised sleep laboratory (Lamont NCI, Medical Systems International, Sydney, Australia). The oxygen saturation recordings were downloaded to an oximetry data analysis program (ODAS, G Harvey, Queensland University of Technology, Brisbane, Australia), whereby artefact free statistical analysis was performed using a Mac II CI computer.

Development/temperament of OSA children

At the time of the overnight sleep study, which was within one month of the clinical assessment, study children were tested using the Griffiths Mental Development Scales[16] ($n = 40$). In addition to an overall developmental quotient, the subscales provide a profile of a number of developmental areas compared to measures such as the Bailey Scales of Development. The shortened versions of the Infant, Toddler and Child questionnaires[17] have strong psychometric properties and were derived by factor analysis based on data from the Australian Temperament Project. Questionnaires were completed by study parents at the time of the sleep study. Common to all three questionnaires were the areas of Rhythmicity, Approachability, and an Easy/Difficult scale. A child was considered to be problematic in an area if they were more than one standard deviation from the mean for the more difficult attribute. These aspects of temperament may reflect behavioural manifestations of OSA.[18]

Parental questionnaire

Detailed questionnaires concerning the perinatal history, the children's health and their development was completed by the parents of the OSA and comparison children.

Perinatal history: Events during the first and second half of the pregnancy including fevers, hypertension, sweating, fatigue, swelling, bleeding, infections, alcohol intake and smoking were recorded. Events at birth included the type of delivery, oxygen requirement, resuscitation and whether the infant cried immediately.

Health: Parental reports of their child's respiratory illnesses during the past year, including chest/ear infections, asthma, hayfever and snoring behaviour were recorded as well as allergies or a family history of allergy.

Current development: A rating by parents of 'average/above average', 'mild difficulty', or 'moderate/severe difficulty' was given for the areas of speech, understanding language, hearing, hand skills, movement/co-ordination, social/play, dressing and eating. The mild and moderate/severe ratings were grouped to form a rating of 'developmental' concern, as very few parents reported 'moderate/severe' concerns.

Other: Maternal education, maternal age and employment were recorded.

Comparison group

Information was available from a concurrent study[19] where the same Parental Questionnaire as described above was administered to parents of 75 children less than 5 years of age attending the Outpatients Fracture clinic (61% male, 39% female, mean age 37 (5) months, range 8–62 months). This was considered an appropriate group for comparison of pregnancy and perinatal data, and the aetiology for fractures should be unrelated to OSA or developmental disorder. Eight (11%) of these children were habitual snorers, that is they snored 'all of the time' or 'almost always' and were therefore excluded from the analyses. Children in the Comparison group had no formal polysomnographic study or Griffiths developmental assessment, and parents did not complete the Temperament Scale.

STATISTICAL ANALYSES

Initially the OSA and comparison children were compared for pregnancy/perinatal risk factors, and parental reporting of development and health concerns as derived from the Parental Questionnaire. Secondly, Griffiths scores and infant temperament ratings were examined within the OSA group in relation to the severity of OSA.

The Chi-square test was used, with Yates correction where appropriate for categorical data, and Student's *t*-test was used to compare the mean Griffiths developmental scores. Where data were not normally distributed, the Mann–Whitney *U*-test was

used. For comparison of means across OSA severity ratings, an analysis of variance was also used. Logistic regression was used to examine possible independent predictors of risk of OSA. A two-tailed *P*-value of less than 0.05 was considered to be statistically significant. Analysis was performed using SPSS PC+.[20]

Ethical approval

This study was approved by the Mater Children's Hospital Research and Ethics Committee.

RESULTS

No significant differences were present between the OSA and the Comparison groups for, gender (68% study males *vs* 58% control males), age distribution (mean age 33 (SD 6) months *vs* 37 (14) months), or maternal education and employment. The mean age of the study mothers was slightly lower than that of the comparison group (mean age 31 (5) years *vs* 33 (6) years, $P = 0.05$).

Complications during pregnancy were increased in the study mothers, with a greater proportion reporting infections, fatigue and increased hospitalisations. Children with OSA were reported as less likely to have cried at birth, and more likely to have required oxygen, resuscitation and admission to a special care nursery. Smoking in early (20% *vs* 22%) and late (22% *vs* 16%) pregnancy was examined in the study and group controls, but the differences were not statistically significant. Asthma, chest infections and ear infections were also significantly more common in the children with OSA (Table 1). All significant predictors from Table 1 for the categories of pregnancy complications (model 1) and birth events (model 2) were examined in separate logistic models with risk of OSA as the dependant variable. Significant predictors from both of these models remained independent predictors of OSA when entered simultaneously into a final logistic model (hospitalised OR 13, 95% CI 2.0–82.8; poor sucking/feeding OR 5.7 CL 1.7–18.9).

Sixty-eight per cent of children with OSA had a family history of allergies compared to 20% of the comparison group ($P < 0.001$). Ninety seven per cent of children with OSA had a family history of snoring, though similar data were unavailable for the Comparison group.

A significantly greater proportion of children in the OSA group were rated by parents as having developmental concerns in the majority of areas evaluated (Table 2). For four of the six developmental areas in Table 2, the relevant subscales of the Griffiths Test for the OSA children could be examined. Maternal ratings of developmental concerns in speech, understanding sentences (Hearing/Speech subscale) and movement (Gross motor subscale), though not play skills (Personal/Social subscale), corresponded closely with the Griffiths subscale scores. Griffiths GQ and subscale scores were compared for the 21 children with mild OSA (OEI ≥ 1, < 5) and the 16 children with moderate or severe OSA (OEI ≥ 5). Scores in overall GQ (106 *vs* 100, $P = 0.1$) and all subscales were consistently lower in the children with moderate/severe OSA, although no differences reached the level of statistical significance.

If children with an OEI ≥ 10 were considered as a separate severe group, there was no statistically significant difference between the mild 106 (11), moderate 102 (10) and severe 99 (15) group means, although GQ declined with increasing severity.

The prevalences of adverse ratings in the temperament areas of Easy/Difficult, Rhythmicity and Approachability were compared between the mild and the moderate/severe OSA groups. No differences were statistically significant. Overall, 11(30%) of the 37 OSA children were rated as having a difficult temperament (more than 1 standard deviation above the mean) which is higher than expected from the general population norms.

As young infants may not show specific developmental delays, the analyses were repeated for parental developmental ratings and Griffiths scores excluding two study infants and three control infants who were less than 12 months of age. No significant changes in the results were found.

Table 1 Comparison of the prevalence of significant maternal pregnancy complications, birth events and childhood illness for neurologically normal OSA children and comparison children

	OSA children ($n = 37$)		Comparison group ($n = 67$)		
	Total number	Problem (%)	Total number	Problem (%)	*P*-value
Pregnancy complications					
Infections	36	17	62	3	0.007
Hospitalised	36	19	62	3	0.007
Fatigue	36	39	60	20	0.04
Birth events					
No immediate cry	32	47	61	13	0.01
Require oxygen	33	30	56	11	0.05
Resuscitation	35	26	53	4	0.008
Admitted to SCN	35	37	63	14	0.03
Poor sucking/feeding	34	41	67	13	0.001
Childhood illness					
Asthma	36	56	67	15	< 0.001
Chest infections	35	70	67	33	< 0.001
Ear infections	35	54	66	20	< 0.001

Totals vary because of missing data/information unknown to mother; SCN = Special Care Nursery.

Table 2 Comparison of the prevalence of maternal ratings of current developmental concerns between OSA children and comparison children

Developmental area	OSA (n = 37) Total group	Concerns (%)	Comparison group (n = 67) Total group	Concerns (%)	P-value
Speech	32	31	66	8	0.002
Understanding sentences	32	28	63	8	0.008
Hearing	36	36	67	0	< 0.001
Play skills	35	20	64	2	0.001
Movement	35	34	65	6	< 0.001
Eating	36	37	65	7	< 0.001

Numbers vary because of missing data.

DISCUSSION

Children with OSA in this study had a higher prevalence of maternal pregnancy complications, perinatal problems, respiratory related health problems and parental reports of current developmental difficulty than children in the comparison group. We found no statistically significant association between the severity of OSA and either the Griffiths score or a rating of more difficult temperament, although there was a consistent trend for lower GQ scores in children with moderate/severe OSA.

Relatively few studies to date have dealt with pregnancy or birth events as risk factors for later OSA in children. Kahn *et al.*[11] examined exposures during pregnancy of mothers whose children had apnoeic events, and reported that increased smoking during pregnancy was significantly related to increased frequency and duration of these events. Study mothers were also more likely to report bleeding during pregnancy. Blurton-Jones *et al*.[21] found an association between increased adverse perinatal biological events in the mothers of children who had frequent night wakings and disturbance of sleep.

The increased rates of adverse pregnancy and perinatal events in mothers of our children with OSA suggest that these may predispose the child to more severe OSA possibly by impaired neural control of the upper airway, although the mechanisms of this association are uncertain. If all women with missing data were assumed to have no perinatal difficulties, then these differences would still be marked and statistically significant. An alternative explanation would be recall bias, with mothers of mothers of children with OSA being more sensitive to recollecting adverse events in pregnancy. It was possible to examine the maternal charts of the eight study children born within the Mater Hospital. Comparison of the maternal reports and the actual birth records confirmed all adverse perinatal reports. We cannot exclude, however, the possibility that selection factors may have operated where children with more medically complex histories or associated behavioural/developmental difficulties were preferentially referred to the Sleep Unit.

More recently, a number of studies have suggested that genetic factors may also predispose the individual to apnoeic events.[22–24] Given the high prevalence of snoring in the family history of our study children, genetic factors should also be considered as a potential determinant of OSA.

Increased respiratory illness in children with OSA is common and has been observed frequently in other studies.[25] Gaultier[10] has suggested that symptoms of OSA are more pronounced at times of intercurrent respiratory illness, and this may have led to preferential referral of children with recurrent respiratory disease. Recurrent middle ear disease is associated with developmental and behavioural difficulties, especially speech and attentional problems[13,26] and may mediate the association between OSA and these outcomes.

In this study, despite exclusion of the neurologically abnormal children, parental reports of mild and moderate/severe difficulty in a number of current developmental areas was significantly increased in contrast to the comparison group. While it is possible that mothers of children who have been diagnosed with a disease are more likely to overidentify problems of behaviour and development in their child, Glascoe and Sandler[27] found that overall parental age-estimates of development in young children were 81% sensitive to likely developmental problems in the areas of fine motor, language, gross motor and behaviour although specificity was lower. Pulsifer *et al.*[28] also support this conclusion and reported that maternal reliability was independent of maternal education and parenting experience. There was also a consistent association between a parental rating of developmental difficulty and lower corresponding Griffiths subscale scores. As mentioned previously, however, children with OSA and associated developmental disorder may be preferentially referred for sleep studies.

The findings of lower GQ and subscales scores on the Griffiths test in children with moderate/severe OSA were not statistically significant and may be due to chance. Due to lack of resources it was not possible to perform polysomnographic and Griffiths studies on control children so that the high prevalence of parental developmental concerns in OSA children could be confirmed by a comparison of the Griffith scores. The limited analyses possible, however of parental concerns and Griffiths subscale scores were suggestive of consistency. The Griffiths scores in the OSA children may be lower than reported, as recent restandardisation of the Griffiths scale in the UK suggests that it overestimates GQ by 11 points.[29] Temperamental or behavioural difficulty in children with OSA has been well recognised.[7,8] Guilleminault *et al.*[6] reported that 40% of a cohort of 25 children with continuous partial obstruction were either aggressive and rebellious or socially withdrawn. If OSA is related to development and temperament, severity of OSA might have been expected to influence the strength of this association. The spectrum of severity of OSA within our sample is similar to that of Carroll *et al.*[15] Study size was limited by the complexity and cost of sleep studies, and though larger than many similar studies in the literature,[2,4] the lack of statistical significance may be a beta error and reflect a lack of power. This particularly needs to be considered as the difference in overall GQ between the mild and moderate/severe group was 6 GQ points, which is half a standard

deviation on the Griffiths Test and may be of clinical significance. Though no association was present with global measures of development assessment, examination of more specific cognitive functions such as memory, vigilance and attention as reported in adult studies[2,3,30] may have resulted in different findings.

In summary, this study suggests that a number of pregnancy, perinatal and respiratory factors may predispose to OSA in neurologically normal children. Mothers of children with OSA were more likely to report developmental concerns and more difficult temperament traits, although the association between severity of OSA and development or temperament was not statistically significant. Because of possible selection bias and lack of polysomnographic data for normal children, findings from this study suggest that there is a need for population-based polysomnographic studies of OSA and control children in association with detailed assessments of development, specific cognitive functions, behaviour and temperament.

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