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The Medical and Mental Health Comorbidities of Children with ADHD in A Sibling Control Design Study

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Abstract

Our study investigates the medical and mental health of children with Attention Deficit Hyperactivity Disorder (ADHD) compared to their non-ADHD sibling. A cross sectional community study of 130 children who met the Diagnostic Statistic Manual IV for ADHD, on stimulant medication for at least a year and their siblings closest in age without the diagnosis of ADHD was completed. The ADHD child was significantly more likely to be diagnosed with psychiatric/developmental and medical disorders in comparison to their non-ADHD siblings. We report significant differences for most psychiatric diagnosis evaluated; medical conditions such as sleep problems and feeding difficulties in infancy and migraine had OR of (OR 4.29; CI 1.85-9.95); (OR 2.68; CI 1.26-5.66) and (OR 2.18; CI 0.62-7.64) respectively. Our findings suggest ADHD children experience considerably higher comorbidities from an early age than their non-ADHD siblings despite their shared genetic and environmental factors; hence requiring significantly more services.

Keywords: ADHD; Mental comorbidities; Medical comorbidities; Siblings

Abbreviations: ADHD: Attention Deficit Hyperactivity Disorder

Introduction

ADHD is a common neuro-behavioural disorder of childhood with a worldwide prevalence estimate of 5% with a male to female ratio of 4:1 [6,21,36,46]. ADHD in the Australian General Paediatric Practice accounts for 18-30%, most frequent diagnosis of all patient presentation [23]. It is established that most patients (76%) with ADHD in Australia are increasingly seen through private paediatric practice than public system [12]. ADHD is characterised by inattention, hyperactivity and or impulsivity that is excessive for the developmental age and impairing functioning in several domains of life (DSM1V). It is a chronic disease that continues into adulthood in 60% of people [14,20], with reduced quality of life [35]. It significantly affects the child's social engagement, educational and career development and financial viability in life [2,5,20].

The aetiology of ADHD is a complex interplay of genetic and non- inherited environmental factors [47]. ADHD has

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a high heritability rate of 75%-79% [15,28]. The main environmental factors described in literature include smoking, alcohol, maternal stress and substance use in pregnancy; low birth weight and prematurity; severe early deprivation, home environment and parenting factors; environmental toxins, dietary deficiencies/surpluses and the presence of unmeasured confounders. A cohort of environmental factors combined with the appropriate gene or epigenetics may explain the developmental process of ADHD [47,48].

High risk siblings of ADHD children followed up in a four year prospective study showed higher rates of disruptive behaviour, anxiety and mood disorders. A survey of Australian paediatric practice in their assessment and treatment of ADHD showed co morbidities may be under diagnosed [12]. The psychiatric comorbidities of ADHD such as conduct disorder, oppositional defiant disorder (ODB), depression, anxiety, learning disability; Tourette's and mental retardation are well described and established in the literature [4,12,17,26,52]. The medical comorbidities that have been described in relation to ADHD include: sleep problems, epilepsy, allergies, injuries, respiratory and ENT diseases and developmental problems [1,4,10,11,16,19,22,24,26,27,29,33,44,49,52].

Our parent study [43], established 92% of the larger sample of ADHD children had comorbidities both mental and physical. There is increased rate of hospitalization in ADHD children compared to controls in early childhood [41] and importantly is the large health burden and economic cost of the disease [5]. Studies with a combined approach to medical and mental health comorbidities and controlling for genetic and environmental factors of ADHD children and their siblings are limited. Our interest in this study is to obtain a parental perspective of the comorbidities of a population of ADHD children as compared to their siblings of a similar genetic and environmental background. Our study examines children with ADHD and their siblings in an Australian intra-familial design using retrospective data in a community referred setting, focusing on their medical and mental health needs. An intra-familial design has the advantage of controlling for shared genetic and environmental variability such as socioeconomic status, family environment; however unshared factors (genetic, environmental or both) will exist based on the degree of siblingship and other uncontrollable factors [51]. Our study is the first Australian study observing and reporting a snapshot health experience comparing an ADHD child and the non-ADHD sibling of an ADHD child.

Methods

Data were collected in a cross-sectional community study between November 2009 and July 2010. This was nested into a wider study that examined ADHD co-morbidities, family stress and effect of medication; pregnancy risk factors and parental mental health [42,43]. As part of this, data were collected comparing ADHD patients with their non -ADHD sibling counterparts.

One hundred and thirty children with ADHD and their siblings were recruited from eight private clinics across Perth, WA. These clinics were selected across the four geographical areas. Overall, ADHD children on stimulants in WA remained stable during the study period [21]. Children with ADHD were eligible if they met the DSM IV criteria or ICD -10 and had commenced treatment at least one year prior to enrolment in study. Ethics approval for the study was obtained from the Human Research Ethics Committee of the University of Western Australia.

The research process was explained to parents and those who gave consent were given a self-report questionnaire to complete. The questionnaire sought information on the child's demographics; ADHD related history and management; doctor- diagnosed medical and psychiatric co-morbidities of child; suspected mental health conditions of the ADHD child; perinatal history, child's early years, engagement in school and need for allied health care which involved physiotherapy, psychology, speech, and occupational therapy. Specific psychiatric co-morbidities such as: depression, anxiety, autism, ODB, obsessive compulsive disorder; and general medical co-morbidities such as injuries, ENT disorders, epilepsy, migraine, food allergy, sleep and feeding disturbances, elimination disorders were assessed. However, provision was made for conditions not included in the above list and characterised as others.

The engagement in school was measured using a 5 point likert scale for how parents quantified their child's enjoyment at school; parental report of school refusal, bullying, repetition of grade, extent of disciplinary measures for disruptive behaviour and suspension/expulsion from school. Similar information was collected for the sibling without ADHD symptoms (based on parental disclosure), closest in age to index child. In addition, the demographic details of parents were collected. All siblings were full siblings, no twins or half siblings were involved in the study. Siblings with a diagnosis of ADHD were excluded for this study. The study had a response rate of 89% and exclusion of thirty

subjects due to partial completion of questionnaire. A total of 130 cases and 130 siblings were examined and their results are presented.

Statistical Analysis

Categorical data was described using frequencies and proportions, and continuous data using medians and ranges or inter quartile ranges. Differences in proportions for medical, mental health conditions and allied therapy requirement was assessed using chi square or fishers exact test (when cell counts were <5). T tests were used to analyse the differences in means between the two groups for characteristics.

Conditional logistic regression was used to produced odds ratios and their 95% confidence intervals and corresponding p value. This method was chosen over unconditional (standard) logistic regression to account for the matching of the children with ADHD with their sibling.

All data was assessed using Stata 14 (College Station, TX: StataCorp LP). Alpha was set as $p<0.05$.

Results

The ADHD group has a mean age of 12.7 (SD 3.4) years and the sibling group 12.58 (SD 5.2) years. Both the ADHD children and their siblings were well matched in age, birthweight and gestational age, however there were more females in the sibling group (Table 1). We considered each ADHD-Sibling pair equally matched for socioeconomic status as they were from the same family. Furthermore, the effect of the parent's background medical condition could not be selectively different in the ADHD-Sibling pair except for the unshared 50% genetic variability which in this study we could not control for. The distribution of selected parameters of the ADHD – Sibling control group is illustrated in Table 1.

	ADHD	Sibling Control
Gender ** Male number (%) Female number (%)	 104 (80.0) 26 (20.0)	 56 (43.1) 74 (56.9)
Mean age (SD) in years	12.7 (3.4)	12.58 (5.2)
Mean birth weight (SD) in grams	3256.2 (661.4)	3329.9 (565.1)
Mean gestational age (SD) in weeks	38.5 (2.9)	39.0 (2.7)

** p value <0.001

Table 1: Distribution of selected parameters of the ADHD-Sibling Pair.

The psychiatric comorbidities in Table 2 identified significant differences for anxiety, depression, obsessive compulsive disorders and an increased prevalence of autism in the ADHD group as compared to the sibling group. Depression by itself was ten times more likely in the ADHD group than the siblings. (CI:1.28 - 78.11, p 0.028) and anxiety was 30 times more likely in the ADHD group compared to the sibling group (CI:9.2-102.5, p<0.001). The sibling group had one reported subject with obsessive compulsive disorder and no oppositional defiant behaviour.

Conditions	ADHD N (%)	Sibling Control N (%)	OR (95%CI)
Depression	11 (9.9)	2 (1.6)	**10.00 (1.28, 78.11) ***
Anxiety	46 (42.2)	3 (2.3)	**30.7 (9.2-102.5) ****
Autism yes suspected yes or suspected	9 (7.0) 6 (4.7) 15 (11.7)	0 (0) 1 (0.8) 1 (0.8)	**15.0 (1.98, 113.56) ****

* p value<0.05; ** p value <0.001

Table 2: Mental health conditions in the ADHD-Sibling Pair.

ODB Oppositional defiant behavior. OCD Obsessive compulsive disorder. NA - fail to converge

Medical conditions such as sleeping problems, migraine and feeding difficulties had odds ratios of 4.3, 2.2 and 2.5 respectively with significant differences, although wide CI due to small numbers. Other common paediatric

conditions reported in children with ADHD such as epilepsy, urinary and fecal incontinence, ear infections, food allergy, constipation, tonsillectomy and grommets insertion were more common in the ADHD compared to the sibling group, however did not reach statistical significance. The ADHD groups were two times likely to have an injury requiring hospital management than the sibling group (OR: 2, p value 0.041). These results were not significantly different when adjusted for gender, age, gestational age or birth weight. See Table 3.

Parental report	ADHD N (%)	Sibling Control N (%)	OR (95%CI) Unadjusted	OR (95%CI) adjusted
All injuries	71 (54.6)	58 (44.6)	1.48 (0.91, 2.41)	1.09 (0.78, 1.96)
Injuries requiring hospital admission	28 (21.5)	15 (11.5)	**2 (1.03, 3.89) ***	**2.24 (1.01, 4.96) ***
Ear Infection	62 (47.7)	54 (41.5)	**1.4 (0.84, 2.34)**	**NA**
Sleeping problems <1- year-old	52 (40.3)	20 (15.4)	**4.3 (2.16, 8.56) ****	**4.29 (1.85, 9.95) ***
Affected by preservatives	50 (40.0)	18 (14.3)	**35 (4.80, 255.47) ****	**NA**
Fussy eater < 1-year old	43 (33.3)	19 (14.6)	**2.5 (1.40, 4.46) ***	**2.68 (1.26, 5.66) ***
Enuresis > 6 years old	28 (21.5)	19 (14.6)	**1.69 (0.85, 3.36)**	**1.08 (0.32, 3.68)**
Constipation	28 (21.5)	18 (13.9)	**1.79 (0.93, 3.44)**	**2.43 (0.97, 6.07)**
Grommets	24 (18.5)	14 (10.8)	**2.25 (0.98, 5.17)**	**1.42 (0.49, 4.11)**
Food allergy	21 (16.2)	11 (8.5)	**2 (0.86, 4.67)**	**1.19 (0.38, 3.71)**
Adenoids removed	17 (13.1)	8 (6.2)	**2.29 (0.94, 5.56)**	**1.71 (0.37, 8.02)**
Migraine	16 (12.4)	7 (5.4)	**2.67 (1.04, 6.81) ***	**2.18 (0.62, 7.64)**
Encopresis > 6 years old	14 (10.8)	6 (4.7)	**2.6 (0.93, 7.29)**	**4.7 (0.48, 45.59)**
Tonsillectomy	13 (10.0)	10 (7.7)	**1.38 (0.55, 3.42)**	**13.44 (0.37, 482.94)**
Epilepsy	5(3.9)	2 (1.5)	**4.00 (0.45, 35.79)**	**NA**

* p value<0.05; ** p value <0.001

Table 3: Medical Conditions in the ADHD-Sibling Pair.

NA - fail to converge a adjusted for gender, age, birth weight and gestation age

All injuries: fractures, laceration-requiring stitches, and head injuries

Allied therapy	ADHD n (%)	Sibling Control n (%)	p value
Speech	56 (44.1)	19 (14.7)	<0.001
Occupational therapy	47 (37.3)	8 (6.2)	<0.001
Physiotherapy	19 (15.1)	1 (0.8)	<0.001
Psychology	20 (16.5)	2 (1.6)	<0.001

Table 4: Allied therapy requirement in the ADHD–Sibling Pair in Primary School.

The requirement for speech therapy, occupational therapy, physiotherapy and psychology services in primary school showed a highly significant difference in the ADHD group as compared with their siblings with p values<0.001. See Table 4.

Children with ADHD were much less likely to enjoy school than their siblings; only 40 percent of ADHD children were reported to enjoy school compared to 82 percent of their counterpart siblings. ADHD children were five times more likely to be bullied (<0.001); sixteen times more likely to be sent to the principal for disruptive behavior (0.001) and twenty-nine times more likely to be suspended (0.001). Eight children of the ADHD group had been expelled compared to none in the sibling group.

Parental report	ADHD n(%)	Sibling Control n(%)	OR (95%CI)
Enjoy School 1 not at all 2 3 a bit 4 5 very much*	 16 (12.7) 9 (7.1) 49 (38.9) 34 (27.0) 16 (12.7)	 3 (2.3) 2 (1.6) 18 (14.1) 37 (28.9) 68 (53.1)	NA
Refused to attend school > 1 month	12 (9.3)	4 (3.2)	4.50 (0.97, 20.83)
Bullied at school >3 months	51 (39.5)	17 (13.4)	**4.56 (2.21, 9.37) ****
Repeated a grade	22 (17.0)	22 (16.9)	1.00 (0.48,2.10)
Sent to principal for disruptive behavior	76 (58.9)	16 (12.4)	**15.75 (35.73, 43.27) ****
Suspended from school	36 (27.9)	7 (5.4)	**29.00 (3.95, 212.89) ****
Expelled from school	8 (6.2)	0 (0)	NA

NA - fail to converge ** p value *<0.001*
Table 5: Schooling in ADHD -Sibling pair.

Discussion

Our hypothesis is that the medical and mental health burden of ADHD children is greater than that of their siblings, even though they have shared genetic and environmental factors. Our findings in this study clearly demonstrate that ADHD children have higher comorbidities than their siblings without ADHD both in physical wellbeing as well as psychological wellbeing; even though the two groups shared some genetic and environmental characteristics. Our study represents a small sample of the ADHD population in WA at the time of the study; however it appeared to be a representative of ADHD presentations to paediatric practice [21].

The ADHD group was significantly affected by common psychiatric conditions such as anxiety and depression; other psychiatric problems such as oppositional defiant disorder and obsessive compulsive disorder were higher in this group. The sibling group had a lower rate of psychiatric conditions than their ADHD counterparts. Previous studies comparing ADHD cases, affected siblings of ADHD cases, non-affected siblings and controls found comparable results [13,30,45,52]. Non-affected siblings as compared to healthy population controls have elevated separation anxiety and poor internalizing problems depending on level of severity of the ADHD children. The lower rate of comorbidities among non-affected siblings as compared to their ADHD siblings may be related to the ADHD component. Future sibling studies designed prospectively will be instrumental to clarify this.

Siblings without ADHD had lesser medical problems and lesser injuries requiring admission. From earlier studies, children with ADHD were more likely to be diagnosed with medical problems such as epilepsy, sleep disturbances, allergic conditions, infections, ENT problems, migraine, constipation, enuresis and encopresis compared with their healthy counterparts [1,10,18,19,22,31-34,44,50]. Our study also identified fussy eating and sleeping difficulties in infancy in the ADHD group, long before the diagnosis of ADHD. Children with ADHD have a higher prevalence of injuries than other children and these increases the younger the child;

they also presented more than controls to the emergency department. A study comparing ADHD children with non-ADHD siblings showed higher rates of accidental injuries in school-aged children with ADHD regardless of sub-type when compared with sex and age matched non- ADHD sibling controls [24,27,40].

Though not significant, children with ADHD in our study were four times more likely to have epilepsy than their siblings. ADHD is 31-40% prevalent in school children with epilepsy [11,22]. In addition, an increased incidence of abnormal EEG patterns has been reported in ADHD children without epilepsy [25,38]. Davis et al. [9] reports that children with ADHD were three times more likely to have epilepsy than their controls, with an earlier onset of seizures and an increased frequency of seizures compared to controls. Enuresis, encopresis, constipation, food allergies have not shown a significant difference in our study, but are still more common in the ADHD group, as supported by other studies [29,31,32,50]. ENT problems such as ear infections and those requiring grommets, enlarged tonsils and adenoids requiring surgical management in our study were reported more commonly in the ADHD group compared to siblings, but also did not meet statistical significance due to small numbers in our study. Other studies have similarly described ENT problems to be frequent amongst ADHD children [1,33,41].

Sleep disordered breathing secondary to adeno-tonsillar obstruction requiring surgical management are important confounders for ADHD diagnosis as they may present similarly to ADHD [39]. In this meta-analysis showed a moderate association between sleep disordered breathing and ADHD was deserved and a moderate improvement was found in ADHD symptoms post adeno-tonsillectomy. The lack of statistical significance in epilepsy, enuresis, encopresis, constipation, food allergies, and ENT disorders in our results as compared to previous studies may be due to recollection bias, a result of the small size or the control cohort type. The higher need for allied health services in the ADHD group possibly illustrates other undiagnosed or associated physical and mental problems encountered in this group compared to their siblings. It is possible that this difference between the two groups could be explained by the ADHD diagnosis, other neurodevelopmental disorder such as autism which is also more common in this group; or other undiagnosed conditions. It is well documented that children with ADHD have an increase in the prevalence of developmental coordination disorder than their siblings [16]. This information was not collected in our study.

School satisfaction and engagement which is an extension of both medical and psychological health is lower in the ADHD group. Like other chronic conditions with functional limitation, the degree of limitation is proportional to academic impact. ADHD specifically and other chronic conditions have been shown to have a significant impact on school performance, irrespective of absenteeism, socio-economic factors and other confounders [8]. This is a vicious cycle resulting in future unemployment, impacting on future health and economic viability and eventually on national economic growth and development. Apart from academic difficulties our study also showed increased bullying, suspension and expulsion from school.

Our study population is a fair representation of ADHD children presenting to paediatric practice in WA and Australia, considering most cases are seen in private practice [12] and also most ADHD cases are diagnosed by Paediatrician in 73%-88% of cases [7,21] . The strength of our study is the intra-familial design which controls for factors which other study designs could not control for. The main limitation of this study is parent recall bias which may affect the distribution of inactive comorbidities across both groups. The small size of the study was limited by the number of available non-ADHD siblings which explains the wide confidence intervals and the failure to converge for some of the analysis. Even though our hypothesis is that the ADHD group would have a higher comorbidity than the sibling group based on earlier studies with population controls, we expected some of the siblings because of shared genetic and environmental background to show some comorbidity expression. A population control as a third group would strengthen the comparison in the delineation of the frequency of these comorbidities and the explanation of the effect of genetic and environmental factors.

The gender ratio which is recurrently inherent in the current rate of diagnosis of ADHD, could have affected our results considering the significant gender distribution of the cohort, however when adjusted for gender there was no substantial migration of results towards or away from significance. It is known that female children with ADHD are underdiagnosed/ diagnosed later [3,37], which raises the possibility of undiagnosed ADHD in the sibling group since it has a higher female ratio. This by itself could not be avoided by the current diagnostic process; however a larger representative sample may reduce this. The lack of doctor disclosure for the non-ADHD siblings is a potential limitation. However, the initial step towards diagnosis is parental report, which in the context of an index diagnosed case raises parental sensitization towards

another diagnosis. Therefore, the ability of parents to report their other child without the disease is possible.

In conclusion children with ADHD have significantly higher mental health, medical and surgical problems; require early allied support compared with their sibling and encounter more challenges at school. We recommend future studies to include prospective interfamilial studies of ADHD children, to provide a better understanding of the role of genetic and environmental factors, protective factors and recognition of early markers in children at substantial risk of ADHD.

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