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Relationship between late preterm birth and expression of attention-deficit hyperactivity disorder in school-aged children: clinical, neuropsychological, and neurobiochemical outcomes

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Abstract: Attention-deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder in school-aged children, and prematurity is a recognized risk factor. Late-preterm birth, which represents 75% of premature births, is associated with ADHD symptoms, impaired cognitive performance, and behavior problems. However, little is known of the characteristics of ADHD associated with late prematurity. The purpose of this study was to compare the clinical, neuropsychological, and neurobiochemical characteristics associated with late-preterm ADHD with those of at-term ADHD.

Methods: Eighty-six children with ADHD, aged 5–13 years, were recruited. They included 20 late-preterm children with ADHD and 66 at-term children with ADHD. The Diagnostic Interview Schedule for Children-IV and the Continuous Performance Test (CPT) were used to evaluate their clinical and neuropsychological characteristics. Proton magnetic resonance spectroscopy was used to measure the ratio of metabolites (glutamate, choline, and N-acetyl-aspartate) to creatine in both the prefrontal and striatal regions as well as the left cerebellum.

Results: The groups did not differ in regards to clinical outcomes. However, the ADHD late-preterm group had worse omissions and commissions T-scores on CPT ($P \leq 0.05$) than the ADHD at-term group. The ADHD late-preterm group also had lower ratios of glutamate in the left prefrontal cortex than the ADHD at-term group ($P \leq 0.05$).

Conclusion: Among children with ADHD, those born at late preterm have lower attention scores as evaluated by CPT and are associated with lower relative concentrations of glutamate in the prefrontal region than those born at term. Etiological factors could play a role in the expression of ADHD.

Keywords: attention-deficit hyperactivity disorder, preterm, neuropsychological, risk factors, magnetic resonance spectroscopy, glutamate, prefrontal cortex

Introduction

Attention-deficit hyperactivity disorder (ADHD) is a common psychiatric disorder of childhood, affecting 5%–10% of school-aged children,[1] and includes symptoms of inattention and/or hyperactivity-impulsivity. Three subtypes of ADHD exist based upon symptom presentation, ie, inattentive (ADHD-I), hyperactive/impulsive (ADHD-HI), and combined (ADHD-C).[2] In addition, ADHD cases commonly present with comorbid disorders. Such disorders can include internalizing conditions, such as anxiety

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or depression, and externalizing ones, such as oppositional defiant disorder.[3] Neurological anomalies can also be found in people with ADHD. For example, brain imaging studies have shown a 5% reduction in the total volume of the brain and cerebellum, as well as dysfunction and biochemical changes in the frontostriatal regions.[4–7]

Several risk factors for developing ADHD have been identified. In particular, prematurity, alone or in interaction with genetic factors, appears to play a major role in the etiology of ADHD.[8] In fact, studies have shown that the prevalence of ADHD is three times higher in preterm than at-term children.[9]

Most studies on the neurodevelopmental consequences of prematurity, such as ADHD, focus on children born before week 34 of gestation. However, maturation of the brain remains incomplete until week 37 of gestation (late preterm); consequently, early as well as long-term complications are frequent. Compared with at-term infants, late-preterm infants have higher frequencies of medical complications, such as respiratory distress, seizures, and higher rates of rehospitalization.[10] Children born late preterm are more than three times as likely as children born at term to exhibit signs of developmental delay or mental retardation.[11] Adams-Chapman[12] showed that by 5 years of age, 13.6% of late-preterm children versus 11.8% of at-term children required special education. Similarly, Huddy et al[13] found that 19% of their sample of 7-year-old children born between 32 and 35 weeks of gestation had an abnormal score on a measure of hyperactivity while 7% needed special education. Gray et al[14] found that 20% of their 8-year-old cohort born at 34–37 weeks of gestation had clinically significant behavior problems.[15] Danish registers showed that 6.4% of children aged 2–18 years and born at 34–36 weeks of gestation had a hyperkinetic disorder.[9]

In further research, Baron et al[16] obtained results from a sample of 3-year-old children and showed that late-term birth was associated with visuospatial, visuomotor, and executive function deficits. In a moderately preterm (32–36 weeks) school-aged sample, van Baar et al[17] found a greater percentage of children exhibiting sustained attention difficulties, behavior problems, and ADHD symptoms than typically found in at-term children.

Accompanying the data showing that late-preterm births are related to subsequent dysfunction in childhood are epidemiological studies reporting an overall increased incidence of late-preterm birth in the general population. Between 1981 and 2003, there was a 31% increase in preterm births in the United States, the largest contribution to this finding was from late-preterm births.[10] In 2002, 75% of premature births and 8% of total births were late preterm.[18] In spite of the evidence of increased risk for ADHD within the premature birth population and the increased incidence of late-preterm birth, little research has targeted the characteristics of ADHD associated with late-preterm birth.

The objective of our study is to compare children with ADHD who were born late preterm (ADHD-lp) with those who were born at term (ADHD-t), using a comprehensive assessment that includes clinical, neuropsychological, and neurobiochemical outcomes.

Materials and methods

Participants

The participants diagnosed with ADHD were recruited from the outpatient child psychiatry clinic of Hotel Dieu de Levis Hospital, Quebec, Canada. The diagnosis of ADHD was given based on the positive presence of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria and a clinical evaluation conducted by experienced child psychiatrists. Eighty-six children with ADHD, aged 5–13 years, were ultimately recruited for the study, 20 of whom were born between 34–36$^{6/7}$ weeks (ADHD-lp) while 66 were born at term (ADHD-t).

All participants were Caucasian, third-generation French Canadians. Children who had an IQ below 70 (according to the Wechsler Intelligence Scale for Children-IV or the Wechsler Preschool and Primary Scale of Intelligence-III) were excluded, as were children diagnosed with a pervasive developmental disorder or psychosis. Lastly, all children were required to stop taking their medication at least 24 hours prior to their study assessment. The local ethics committee approved the study, and all parents provided signed informed consent to participation. Likewise, children expressed their agreement to participate. Research personnel who completed the evaluation sessions were blinded to the birth status of each participant.

Assessments

Pregnancy and birth complications

The Kinney Medical and Gynecological Questionnaire[19] was used during an interview with the mothers to collect information on obstetric and neonatal complications. The participants' responses on this questionnaire were scored using the McNeil-Sjöström Scale.[20] This risk scale classifies the severity of complications during pregnancy, labor, delivery, and the neonatal period along a series of levels ranging from 1 to 6 (6 being the most severe). The severity weights are intended to reflect the inferred probability of

harm to the offspring, with special focus on the offspring's central nervous system. The total score for neonatal complications was calculated without including the score for premature birth because premature birth is itself one of the neonatal complications noted in the McNeil-Sjöström Scale. The perinatal complications were measured because they could interfere with premature birth outcomes.[21]

Clinical outcome

The Diagnostic Interview Schedule for Children Version IV (DISC-IV) is a semistructured interview based on the DSM-IV criteria. The parent version was used to obtain information on each child participant's clinical ADHD characteristics.[22] Scores were obtained for inattentive, hyperactive-impulsive, and total ADHD symptoms. Additionally, the presence or absence of comorbid disorders was noted, and global functioning scores were recorded.

Neuropsychological outcome

Attentional processes were assessed using the Conners' Continuous Performance Test Version II (CPT). The CPT is a 14-minute computerized test that assesses inattentiveness, impulsivity, and vigilance. The computer program yields T-scores which are age-standardized to a general population (mean ± standard deviation = 50 ± 10) for errors of omission (failing to respond when the child should), errors of commission (responding when the child should not), and hit reaction time (HRT, change in the child's reaction time between inter-stimuli intervals).[23,24]

Brain-imaging measures

Proton magnetic resonance spectroscopy (^{1}H-MRS) is a noninvasive technique increasingly used in cases of ADHD. It allows the study of in vivo brain metabolites.[25] All patients underwent a brain ^{1}H-MRS, performed with a GE Signa 1.5 T scanner operating at 63.85 mHz (General Electric Medical Systems, Waukesha, WI). The location of the voxels was determined from T1-weighted spin echo images in an axial plane. Spectra were acquired from 8.0 cm^3 voxels localized in five different regions of interest, ie, the left and right prefrontal areas, the left and right striatal areas, and the left cerebellum. For voxel location, we used predetermined anatomical parameters (striatum area, ie, the posterior portion of the head of the caudate nucleus according to the anteroposterior axis; prefrontal area, ie, over the ones determining the striatum voxels; and cerebellum, ie, approximately 3 mm laterally from the ledge of the fourth ventricle). After location of each region of interest, we used the GE Probe protocol, which comprises a suppression of the water signal with the CHESS followed by detection of the proton signal using the PRESS pulse sequence. The acquisition parameters were as follows: repetition time, 1500 msec; echo time, 30 msec; number of acquisitions, 128; spectral width, 2000 Hz; number of points, 1024; total acquisition time, about 40 minutes. With these acquisition conditions, the signal/noise ratio was 12 or more for the main signals (ranging from 12 to 28, depending on the region). The MRS data were analyzed using the LCModel software, version 6.0,[26] and metabolite ratios for N-acetylaspartate/creatine (NAA/Cr), choline/Cr (Cho/Cr), myo-inositol/Cr (mI/Cr), glutamate (Glu/Cr), and glutamate-glutamine/Cr (Glx/Cr) were calculated. Before participating in the MRS, children were invited to participate in sessions with an MRS simulator to become familiar with the noises and conditions of the scanner. Despite the scanner simulation sessions, not all brain regions could be assessed for all participants. Furthermore, three participants were excluded from the MRS because they had not stopped their medications. Brain-imaging was performed in 12 children with ADHD-lp and 54 children with ADHD-t.

Statistical analysis

The analyses were performed using SPSS version 12.0 (SPSS Inc, Chicago). Independent *t*-tests were used to compare the clinical characteristics between two groups. To compare the neuropsychological and biochemical data between the groups, we used analysis of covariance with IQ as a covariate. For all tests, statistical significance was set at $P < 0.05$. Corrections for multiple comparisons were not performed to avoid missing potential effects.

Results

General characteristics and perinatal complications

Table 1 summarizes the general and perinatal characteristics of the two groups. Age, gender, and scores for perinatal complications were similar between the two groups. The IQ score, the gestational age, and the birth weight were lower in the ADHD-lp group than in the ADHD-t group.

DISC-IV characteristics

There was no difference between groups in DISC-IV total ADHD symptoms, ADHD subtype repartition, comorbid diagnoses, or the impact on functioning (Table 1). There was no significant between-group difference in comorbidities for oppositional defiant disorder or conduct disorder. Oppositional defiant disorder was present in 30% and 36%

Table 1 Demographic and clinical characteristics of late-preterm ADHD (ADHD-lp) and at-term ADHD (ADHD-t) children

Characteristics	Mean (SD)		*P*-value
	ADHD-lp n = 20	ADHD-t n = 66	
Age, years	9.06 (2.41)	9.28 (1.92)	0.67
Ratio boys/girls	11/9	52/16	0.04
Global IQ	93.30 (8.66)	100.13 (14.22)	0.04
Birth weight, g	2861 (424)	3426 (453)	0.000
Perinatal complication scores	11.83 (6.18)	12.17 (6.23)	0.84
DISC IV-total ADHD symptoms	12.40 (4.64)	12.73 (4.34)	0.77
ADHD subtypes (C/I/H/NS), %	30/40/5/25	36/40/4/22	NS
DISC IV comorbidities, %			
(ODD/CD/AD)	30/0/90	36/9/53	0.62/0.16/0.03*
DISC IV-dysfunction scores	8.45 (3.94)	8.27 (3.98)	0.19

Note: *$P < 0.05$.
Abbreviations: ADHD, Attention deficit hyperactivity disorder; IQ, intellectual quotient; DISC IV, Diagnostic Interview Schedule for Children Version IV; C, combined; I, inattentive; H, hyperactive/impulsive; NS, not specified; ODD, oppositional defiant disorder; CD, conduct disorder; AD, anxiety disorder; n.s., not significant.

of cases in the ADHD-lp and ADHD-t groups, respectively ($P = 0.62$), while conduct disorder was documented in 0% versus 9% of cases, respectively ($P = 0.16$). However, there were significantly more anxiety symptoms in the ADHD-lp group (90%) than in the ADHD-t group (53%, $P = 0.03$).

CPT characteristics

Children in the ADHD-lp group had significantly higher omissions T-scores [F (1, 75) = 4.65, $P = 0.03$] and commission T-scores (F [1, 75] = 4.30, $P = 0.04$) than children in the ADHD-t group. On the other hand, there was no significant difference between the groups in the hit reaction time T-scores (F [1, 75] = 1.19, $P = 0.27$, Table 2).

Brain function characteristics

The mean metabolite ratios for the five regions studied are reported in Table 3. The Glu/Cr in the left prefrontal region was significantly lower ($P = 0.02$) in the ADHD-lp group than in the ADHD-t group (mean [SD] = 1.27 [0.29] and 1.45 [0.23], respectively). There was no difference between groups concerning the concentrations measured in the right prefrontal, left and right striatum, and the left cerebellar regions.

Table 2 Conner's Continuous Performance Test t-scores for late-preterm ADHD (ADHD-lp) and at-term ADHD (ADHD-t) children

	Mean (SD)		*P*-value
	ADHD-lp n = 20	ADHD-t n = 66	
Omissions T-score	63.20 (29.49)	52.10 (8.93)	0.01*
Commissions T-score	54.05 (8.16)	50.09 (13.37)	0.04*
Hit reaction time T-scores	53.84 (16.43)	49.16 (10.21)	0.13

Note: *$P < 0.05$.
Abbreviations: ADHD, Attention deficit hyperactivity disorder; SD, standard deviation.

Discussion

In a population of school-aged ADHD children and at the clinical level, our study found no differences in the characteristics of ADHD or in associated comorbid disorders between late-preterm ADHD children (ADHD-lp) and those who were born at-term (ADHD-t). However, ADHD-lp children did exhibit significantly more anxiety symptoms (but did not meet DSM IV criteria for anxiety disorder). At the neuropsychological level, ADHD-lp children showed less ability to sustain attention as measured by the CPT. At the neurobiochemical level, ADHD-lp children showed lower brain levels of glutamate in the left prefrontal cortex.

To our knowledge, there have been no previous studies of late-preterm children diagnosed with ADHD. However, in children without a previous ADHD diagnosis, there are some studies of ADHD symptoms or hyperkinetic symptoms in mid-term and late-preterm children. For ADHD symptoms, our results are consistent with previous studies in the healthy late-preterm population. Gurka et al,[27] in a large sample of healthy late-preterm children aged 4–15 years, reported no behavioral or emotional differences from at-term children using the Child Behavior Checklist.[28] However, van Baar et al[17] used a school-aged, mid-to-late preterm sample and the same questionnaire, and reported ADHD problems with different symptom characteristics as a function of the respondent. Specifically, mothers of preterm children reported more attention deficit and hyperactivity than mothers of at-term children, whereas teachers reported only attention problems. The authors also identified comorbid disorders, but did not find any significant increase in externalizing behavior problems compared with at-term subjects. However, they did identify more internalizing problems in the preterm group,

Table 3 Metabolite concentration ratios obtained from magnetic resonance spectroscopy in different brain regions in late-preterm ADHD (ADHD-lp) and at-term ADHD (ADHD-t) children

	Metabolite	Mean (SD)		*P*-value
		ADHD-lp n = 20	ADHD-t n = 66	
Left prefrontal cortex	Glutamate	1.27 (0.29)	1.45 (0.23)	0.02*
	Choline	0.29 (0.04)	0.30 (0.04)	0.54
	N-acetyl aspartate	1.42 (0.17)	1.43 (0.16)	0.84
Right prefrontal cortex	Glutamate	1.54 (0.31)	1.44 (0.20)	0.16
	Choline	0.30 (0.04)	0.30 (0.03)	0.86
	N-acetyl aspartate	1.46 (0.38)	1.41 (0.16)	0.46
Left striatum	Glutamate	1.29 (0.19)	1.28 (0.17)	0.92
	Choline	0.23 (0.02)	0.23 (0.03)	0.68
	N-acetyl aspartate	1.16 (0.17)	1.18 (0.16)	0.78
Right striatum	Glutamate	1.24 (0.12)	1.32 (0.25)	0.27
	Choline	0.24 (0.02)	0.24 (0.03)	0.91
	N-acetyl aspartate	1.16 (0.16)	1.20 (0.18)	0.57
Left cerebellum	Glutamate	0.96 (0.21)	1.02 (0.16)	0.30
	Choline	0.26 (0.01)	0.26 (0.03)	0.98
	N-acetyl aspartate	1.09 (0.16)	1.06 (0.13)	0.50

Note: *$P < 0.05$.
Abbreviations: ADHD, Attention deficit hyperactivity disorder; SD, standard deviation.

which is consistent with the increased number of anxiety symptoms in the ADHD-lp group found in our study. In our study, except for anxiety symptoms, the absence of differences in clinical characteristics and comorbid disorders among late-preterm children and those born at-term could be specific to the ADHD population because all of our participants had an ADHD diagnosis.

In school-aged late-preterm non-ADHD children, using the Bourdon-Vos test, van Baar et al[17] found lower sustained attention performance in late-preterm children than in controls. Gurka et al,[27] using a subset of the Woodcock-Johnson Psycho-Educational Battery in healthy late-preterm children, reported no differences from at-term children. In late-preterm non-ADHD studies, differences in sample characteristics (age, presence or lack thereof of medical complications) and instruments used to measure cognitive performance could explain the discrepant results. Once again, the difference between our results and those from other healthy late-preterm studies could be explained by the previous study comparisons of non-ADHD premature children with those born at term without ADHD, whereas we investigated only children with ADHD.

In our study, ADHD-lp children had lower Glu/Cr in the left prefrontal region than children with ADHD-t. The fact that this result was observed only in the left prefrontal cortex is difficult to interpret because this is the first MRS study on preterm ADHD, to the authors' knowledge. Nonetheless, MRS studies in at term ADHD reported left,[29] right,[30] and also two-sided[31] abnormalities in the prefrontal cortex.

In many prior studies, glutamate concentration in the prefrontal area was shown to be higher in ADHD children compared with controls.[32–34] Glutamate is a very important excitatory neurotransmitter in the cortico-striato-cerebellar circuit.[35] MRS studies in humans show that 70%–80% of glucose consumption is used to feed the cycle of glutamate in the resting brain.[36] Our results showing decreased prefrontal glutamate along with worse attention problems in ADHD children born late preterm fits with the energetics hypothesis of ADHD. In this hypothesis, ADHD cognitive dysfunction arises from inefficient and inconsistent neural transmission of information due to a deficient energy supply.[37]

However, our results contradict those from some other studies of at-term ADHD children. For example, Carrey et al[38] reported that the ratio of Glu/Cr decreased after pharmacological treatment, suggesting that clinical improvement may be associated with lower concentrations of these metabolites in the regions of interest. In a recent prospective study conducted in Indonesia, Wiguna et al[31] found a significant decrease in metabolites in the prefrontal cortices of children with ADHD after administration of long-acting methylphenidate for 12 weeks. These differences could be explained by the differences in study populations because all the children from the reported studies were born at term. Also, ADHD has a high genetic component.[39] Our study included only three-generation French-Canadian participants. Differences between our results and those of other studies could also be explained by differences in the genetic backgrounds of the study populations.

Strengths and limitations of the study

Our study has some limitations that must be considered when interpreting the results. First, the relatively small sample size may have limited our ability to detect all neurobiochemical differences between the two groups. Furthermore, regarding the use of medication prior to the study assessments, despite stopping the medication for all children during the study, the fact remains that some children had been previously exposed to different medications over different durations. These differential exposures could themselves have led to long-term neurobiochemical changes that we could not have evaluated. Another limitation is that the Kinney Medical and Gynecological Questionnaire was based on information from the mothers. The reliance on a retrospective maternal interview is a limitation, but it is the case for almost all studies of maternal lifestyle during pregnancy.[40] Also, it has been reported in the literature that mothers usually tend to under-report perinatal complications.[41]

Despite these limitations, our study has several strengths. It is the first study to compare late-preterm ADHD children directly with at-term ADHD children. Additionally, the homogeneity of the sample permitted good control of a number of confounding variables. In particular, as mentioned in other studies, it is often difficult to disentangle the influence of isolated premature birth from other perinatal complications.[42] The lack of a significant difference in perinatal complications between the two groups helped to isolate the late prematurity births and to understand better the influence of late-preterm birth on the characteristics of ADHD. Our genetically homogeneous population of third-generation French Canadians also had limited genetic variability. Further, it is important to note that methodologically, all assessments were conducted in a blinded manner as to the status of prematurity. Finally, our study provides an overview of ADHD from a clinical perspective as well as from a neurobiochemical perspective via brain-imaging data.

Conclusion

Our results suggest that late-preterm children with ADHD may present a worse attention profile than children with ADHD born at term. This profile is associated with lower glutamate levels in the prefrontal region. The identification of neuropsychological and neurobiochemical characteristics of ADHD in regard to etiological factors, including premature birth, may allow adaptation of diagnostic, therapeutic, and preventive strategies to develop more effective interventions and follow-up for this common disorder.

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Disclosure

The authors report no conflicts of interest in this work.

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