ORIGINAL ARTICLE

Gestational age, birth weight, and the risk of hyperkinetic disorder

K M Linnet, K Wisborg, E Agerbo, N J Secher, P H Thomsen, T B Henriksen

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See end of article for authors' affiliations

Correspondence to: Dr K M Linnet, Perinatal Epidemiology Research Unit, Department of Obstetrics and Pediatrics, Aarhus University Hospital, Skejby, DK-8200 Aarhus N, Denmark; kmlinnet@ki.au.dk

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Aims: To study the association between gestational age and birth weight and the risk of clinically verified hyperkinetic disorder.
Methods: Nested case-control study of 834 cases and 20 100 controls with incidence density sampling.
Results: Compared with children born at term, children born with gestational ages of 34–36 completed weeks had a 70% increased risk of hyperkinetic disorder (rate ratio (RR) 1.7, 95% confidence interval (CI) 1.2 to 2.5). Children with gestational ages below 34 completed weeks had an almost threefold increased risk (RR 2.7, 95% CI 1.8 to 4.1). Children born at term with birth weights of 1500–2499 g had a 90% increased risk of hyperkinetic disorder (RR 1.9, 95% CI 1.2 to 2.9), and children with birth weights of 2500–2999 g had a 50% increased risk (RR 1.5, 95% CI 1.2 to 1.8) compared with children born at term with birth weights above 2999 g. The results were adjusted for socioeconomic status of the parents, family history of psychiatric disorders, conduct disorders, comorbidity, and maternal smoking during pregnancy. Results related to birth weight were unchanged after adjusting for differences in gestational age.
Conclusions: Children born preterm, also close to term, and children born at term with low birth weights (1500–2499 g) have an increased risk of clinically verified hyperkinetic disorder. These findings have important public health perspectives because the majority of preterm babies are born close to term.

Previous studies show that children born below 28 completed weeks of gestation have an increased risk of attention–deficit hyperactivity disorder (ADHD),[1–4] and cognitive and behavioural deficits.[5] However, most preterm children are born with higher gestational ages of 28–36 completed weeks. Whether premature delivery at 28–36 completed weeks of gestation increases the risk of clinically verified ADHD is unknown. Additionally, no previous study on birth weight and hyperkinetic disorder (HKD) or clinically verified ADHD has been conducted among children born at or above term (gestational age of 37 completed weeks or more), but previous findings indicate that intrauterine growth retardation (IUGR) at term may have long term effects on growth and development.[6]

HKD and ADHD are characterised by inattention, hyperactivity, and impulsivity.[7] HKD measured in accordance with ICD-10[8] is one of the most prevalent mental illnesses in child psychiatry (1–2%), and HKD is the clinical correlate to ADHD combined type.[9] New findings show that HKD is the fourth (7.3%) most frequent discharge diagnosis in child psychiatry in Denmark; this percentage is increasing.[10]

Our aim was to study the association between prematurity (gestational age 26–36 completed weeks of gestation) and clinically verified HKD. We also studied the association between birth weight in term born children and the risk of clinically verified HKD.

METHODS

Subjects and data assessment

We conducted a nested case-control study based on data from four Danish longitudinal registers: the Danish Psychiatric Central Register,[11] the Danish Medical Birth Registry,[12] the Integrated Database for Labour Market Research (the IDA database),[13] and the Danish Civil Registration System.[14] The Danish Civil Registration System contains a specific personal identification number for all individuals residing in Denmark which also allows linkage to parents and siblings.[14] The personal registration number enables linkage between information in all the national registers.

The Danish Psychiatric Central Register covers all inpatient admissions and outpatient contacts (from 1995) at Danish psychiatric departments. The register includes cumulative records and discharge data, dates, and diagnoses.[11] From 1994, the diagnoses are in accordance with the International Classification of Diseases (ICD), 10th edition;[8] before 1994, the ICD, 8th edition. The Danish Medical Birth Register holds detailed information on all births in Denmark,[12] provided by the midwife present at the delivery. The IDA database contains longitudinal information on labour market affiliation for the total population and sociodemographic data. Continuous annually updated information is available and missing data occur only if the father is dead, unknown at birth, or has immigrated.[13]

This study includes all children born between 1980 and 1994 and registered in the Danish Psychiatric Central Register until the end of December 1999 with HKD as their main diagnosis (n = 834): disturbance of activity and attention (F90.0; n = 524), equivalent to ADHD combined type; hyperkinetic conduct disorder (F90.1; n = 194), equivalent to ADHD with conduct disorder; other hyperkinetic disorders (F90.8; n = 10), equivalent to ADHD inattentive type and hyperkinetic disorder; unspecified (F90.9; n = 106), equivalent to ADHD other types.

The diagnostic groups of children with HKD were categorised as mutually exclusive. If the child had been admitted to a psychiatric department or an outpatient clinic more than once and appeared in the register under different HKD diagnoses, the child was registered with the first

Abbreviations: ADHD, attention–deficit hyperactivity disorder; CI, confidence interval; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; HKD, hyperkinetic disorder; IUGR, intrauterine growth retardation; ICD-8, International Classification of Diseases, 8th edition; ICD-10, International Classification of Diseases, 10th edition; IDA database, Integrated Database for Labour Market Research; RR, rate ratio

diagnosis. To increase external validity, all children with childhood autism, Asperger's syndrome, other pervasive developmental disorders (F84.0–F84.9; 308.0), and mental retardation (F70–F79; 312–315) were excluded. Other comorbidities were allowed; 279 (33%) had other diagnoses. Specific developmental disorders of speech, language, scholastic skills, and motor function (F80.0–F89.3) were the most commonly recorded first subsidiary diagnosis (165 cases; 20%).

By using a nested case-control design, based on the total Danish population, each of the 834 case children with HKD was matched with a random sub-sample of 25 single born children of the same gender, born at the same date, alive and undiagnosed at the particular date the case child was diagnosed.[15 16]

Gestational age, measured in completed weeks (26–44), was reported to the Danish Medical Birth Register by the midwife present at the delivery on a mandatory coding sheet. Gestational age was based on either early fetal ultrasound measures or detailed information on the woman's last menstrual period. Gestational age was categorised into the following groups: 26–33, 34–36, 37–39, 40–42, and 43–44 completed weeks. Gestational age between 40 and 42 weeks was used as the reference. Gestational age below 37 completed weeks was defined as preterm delivery; gestational age below 34 weeks was defined as very preterm delivery.

Birth weights between 690 and 5990 grams were categorised into the following groups: 690–1499, 1500–2499, 2500–2999, 3000–3999, and 4000–5990 g. Birth weights between 3000 and 3999 were used as the reference. A proxy measure of intrauterine growth retardation (IUGR) at or above term (37 completed gestational weeks or more) was defined as birth weight less than 2500 grams. The difference between the mean birth weight adjusted for gestational age among cases and controls was also calculated.

Only subjects with valid information on gestational age and birth weight were included in the final analyses. The final dataset consisted of 834 cases with HKD and 20 100 controls.

Information on hospitalisations and outpatient contacts of cases, controls, parents, and siblings was obtained from the Danish Psychiatric Central Register.[11] Psychiatric data were obtained at the time the cases and the controls were defined. Socioeconomic data on the parents were obtained from the IDA database[13] at the time of birth of the children.

The national and local ethics committees and the Danish Data Protection Committee approved the study.

Statistical analysis

The association between gestational age, birth weight, and HKD (table 1) was calculated as a rate ratio (RR) with 95% confidence intervals (CI).[15]

Potential confounding factors such as socioeconomic factors, parental age, parity (table 2) and familial psychopathology were included one at a time in a multiple conditional logistic regression model, in keeping with Greenland's suggestion.[17] In the final model (table 3), the potential confounding factors (socioeconomic factors, parental age, and familial psychopathology) were included at the same time based on the a priori assumption that they all might confound the results.[16] Information on missing values for each variable was included as a separate dummy variable in all analyses.

Next, we restricted the analysis to children with family members without a history of mental disorders. Furthermore, analyses were restricted to children with HKD without conduct disorder and with no recorded comorbidity other than comorbid disorders that are typically related to HKD (i.e. specific developmental disorders of speech, language, scholastic skills, and motor function (F80.1–F83.9)). Finally, analyses stratified on gender were performed.

RESULTS

Gestational age and HKD

Compared with children born at term, children with gestational ages between 34 and 36 completed weeks had an 80% increased risk of HKD, and children with gestational ages below 34 completed weeks had a threefold increased risk (unadjusted results) (table 1).

Birth weight and HKD

Among children born at 37 completed weeks of gestation, the mean birth weight was lower among cases compared with controls (unadjusted difference −98 g; 95% CI −134 to −61). Children born at term with birth weights between 1500 and 2499 g had more than a twofold increased risk of HKD compared with children born at term with birth weights above 2999 g, whereas children with birth weights between 2500 and 2999 g had a 70% increased risk (unadjusted results) (table 1).

Table 1 Univariate association between gestational age (cases = 834; controls = 20 100) and birth weight at term (cases = 763; controls = 17 625) and the risk of hyperkinetic disorder

	Controls n = 20 100	Cases n = 834	
Gestational age (wk)			
<34	298	34	3.1 (2.2–4.5)
34–36	544	37	1.8 (1.3–2.6)
37–39	6629	298	1.2 (1.0–1.4)*
40–42	12365	456	1
43–44	264	9	0.9 (1.0–1.4)
Children born at 37–41 completed weeks of gestation	**Controls n = 17 625**	**Cases n = 763**	
Birth weight at term (g)			
<1500	1	0	–
1500–2499	288	27	2.4 (1.6–3.6)
2500–2999	1888	127	1.7 (1.4–2.0)
3000–3999	12099	478	1
4000–5990	3349	131	1.0 (0.8–1.2)

Results presented as rate ratios (RR) with 95% confidence intervals (CI) from a conditional logistic regression model.
*p<0.05.
†Cases and controls are matched for age, sex, and date of birth.

Table 2 Univariate associations between socioeconomic characteristics of the parents at the time of delivery of the child and risk of the child developing hyperkinetic disorder

	Controls	Cases	Mother RR (95% CI)	Controls	Cases	Father RR (95% CI)
Years of schooling after basic school†						
3+	9968	303	1	11688	439	1
<3	9400	521	1.8 (1.6–2.1)	6960	376	1.4 (1.2–1.6)
Annual income quartile‡						
Highest	4673	165	1	6122	187	1
Second highest	5353	211	1.1 (0.9–1.3)	5333	230	1.4 (1.1–1.7)
Second lowest	5522	215	1.1 (0.9–1.4)	4678	210	1.5 (1.2–1.8)
Lowest	4503	241	1.5 (1.2–1.8)	3696	187	1.6 (1.3–2.0)
Employed§						
Yes (included students)	10472	322	1	13847	485	1
No	9422	496	1.7 (1.5–2.0)	5982	329	1.5 (1.3–1.8)
Cohabitant status¶						
Married	11890	389	1	11928	392	1
Cohabitant with common children	5920	237	1.2 (1.0–1.4)*	5930	238	1.2 (1.0–1.4)*
Cohabitant without common children	666	47	2.1 (1.6–3.0)	692	52	2.3 (1.7–3.1)
Single	1574	158	3.0 (2.5–3.7)	1269	132	3.1 (2.5–3.8)
Age in years††						
<20	612	50	2.3 (1.7–3.2)	96	4	0.9 (0.3–2.6)
20–24	4834	300	1.7 (1.5–2.1)	2108	157	1.7 (1.4–2.1)
25–29	8185	288	1	6447	279	1
30–34	4703	159	0.9 (0.8–1.1)	6435	210	0.7 (0.6–1.1)
⩾35	1766	37	0.6 (0.4–0.8)	4853	169	0.8 (0.6–0.9)
Parity						
Primiparity	9415	414	1			
Multiparity	10685	420	0.9 (0.8–1.02)			

Results presented as rate ratios (RR) with 95% confidence intervals (CI) from a conditional logistic regression model.
Cases = 834; controls = 20 100.
Cases and controls are matched for age and sex.
*$p<0.05$.
Missing information for mothers and fathers respectively: †(742 and 1471); ‡(51 and 291); §(222 and 291); ¶(53 and 301), ††(paternal age 176 missing).

Gender and age

Of the 834 children with HKD, 750 (90%) were boys. The increased risk of HKD was basically the same in both genders, but analyses on girls only yielded very wide confidence intervals as most of the cases were boys. The age of the children at the time of diagnosis varied between 2 and 18 years (median 8.8; interquartile range 3).

Social factors, previous admissions, family history of psychopathology

Single parent families, disadvantageous social factors, and young age of the parents were associated with an increased risk of HKD in the offspring; the effect of the income level of the father was generally higher than for the mother (table 2).

Previous psychiatric admissions and contact as outpatients of the cases and the controls (RR 21.7, 95% CI 17.0 to 27.5) and psychopathology in the immediate family, measured as admissions to psychiatric hospitals or departments or as outpatient contacts for the mother (RR 2.6, 95% CI 2.1 to 3.3), the father (RR 2.1, 95% CI 1.7 to 2.7), or siblings (RR 3.9, 95% CI 3.0 to 5.1) increased the risk of HKD.

Adjustments for social factors, history of psychiatric disorders in the parents and siblings, and parental age did not change the results substantially (table 3). The small changes in the risk estimates were due to a joint effect from all the variables under study and not accounted for by a single variable. When the results on birth weight in table 3 were adjusted for gestational age in weeks, the results were also unchanged (adjusted difference −94 g; 95% CI −143 to −45). For both exposures under study, a dose-response relation was present

Taking into account previous admissions and outpatient contacts and the time period since the last admission before the diagnosis, the results remained unchanged (data not shown). The results were essentially unchanged after restriction to children with parents or siblings without psychiatric admissions and contact as outpatients, thereby excluding 184 cases and their controls (data not shown).

Conduct disorder and other comorbidity

Excluding cases and their controls with conduct disorders either as main diagnosis (F90.1; 194 cases) or as subsidiary diagnoses (F90.1, 91.1, F91.3, F91.9; 13 cases) also failed to change the results. Exclusion of the 206 children with HKD (and their matched controls) with comorbid disorders other than specific developmental disorders of speech, language, scholastic skills, or motor function recorded as subsidiary diagnoses did not change the results.

Excluding children of parents with a history of mental disorders, children with hyperkinetic conduct disorder (F90.10), and children with other comorbid disorders except for specific developmental disorders (F80.0–F89.3) did not change the results (table 3). The mean birth weight remained lower among cases compared with controls.

Maternal smoking during pregnancy and gestational age

Among children born between 1991 and 1994 (n = 3935, n = 170), information on maternal smoking status was available (smoker, non-smoker).[18] When the analysis of preterm delivery and HKD was performed among non-smokers (n = 2443; n = 65), the risk was still increased (RR 4.1, 95% CI 1.4 to 11.8).

DISCUSSION

This large population based study showed that preterm delivery near term and proxy measures of intrauterine growth in children born at or above term increase the risk of HKD.

Strengths and weaknesses

The longitudinal registers in Denmark provide detailed information on each individual. Our findings were based on

Table 3 Adjusted associations between gestational age (cases = 834; controls = 20 100), and birth weight at term (cases = 763; controls = 17 625), and the risk of hyperkinetic disorder

	Controls n = 20 100	Cases n = 834	Adjusted RR (95% CI)	Controls† n = 10 253	Cases† n = 460	Adjusted* RR (95% CI)
Gestational age (wk)						
<34	298	34	2.7 (1.8–4.1)	152	20	3.3 (2.0–5.4)
34–36	544	37	1.7 (1.2–2.5)	270	19	1.6 (0.99–2.5)
37–39	6629	298	1.1 (0.9–1.3)	3321	166	1.2 (1.0–1.5)*
40–42	12365	456	1	6378	251	1
43–44	264	9	1.0 (0.5–2.0)	132	4	0.7 (0.3–2.2)
Children born at 37 completed weeks of gestation or more	**Controls n = 17 625**	**Cases n = 763**		**Controls† n = 8994**	**Cases† n = 421**	
Birth weight at term (g)						
<1500	1	0	–	1	0	–
1500–2499	288	27	1.9 (1.2–2.9)	131	12	1.7 (0.9–3.2)
2500–2999	1888	127	1.5 (1.2–1.8)	946	75	1.7 (1.3–2.3)
3000–3999	12099	478	1	6204	269	1
4000–5990	3349	131	1.0 (0.9–1.3)	1713	65	0.9 (0.7–1.2)

Results presented as rate ratios (RR) with 95% confidence intervals (CI) from a conditional logistic regression model.
*$p<0.05$.
†Cases and controls are matched for age, sex, and date of birth and adjusted for parental socioeconomic data and parental age. Excluded are children of parents with history of mental disorders (141 cases and their controls), children with hyperkinetic conduct disorder (F90.10) as main and 1st and 2nd subsidiary diagnosis, and other comorbid disorders except for specific developmental disorders (F800–F893) (233 cases and their controls).

all single born children without pervasive developmental disorders born during a 14 year period and registered with HKD as a main diagnosis. The controls were randomly selected from births during the same period. This procedure reduces problems with selection bias and optimises external validity.

Our large population based sample and prospective collection of information on gestational age and birth weight eliminate the risk of parental recall problems, which may result in differential misclassification. We were also able to adjust for several potential confounding factors that previously were poorly controlled. Adjustment for genetic predisposition to mental disorders is an important advantage over previous studies.[1–4] These adjustments reduce the possibility that genetic factors explain our findings.[19] We are, however, aware that our adjustment for genetic predispositions may be incomplete because information on personality traits was unavailable.

Validation studies of the variables in the Danish National Birth Register show a high validity regarding gestational age in the time period under study.[20] We used birth weight less than 2500 grams at or above term as a proxy measure of intrauterine growth retardation. However, intrauterine growth is difficult to conceptualise from the birth weight and gestational age at birth and our results on intrauterine growth retardation should therefore be taken with caution.[21]

The diagnosis of HKD follows international guidelines,[22] but the validity of HKD in the Psychiatric Case Registry and the prevalence of HKD in Denmark remains unknown. By excluding subjects with comorbidity unrelated to HKD, we examined whether our results could be explained by comorbid disorders. Apparently they were not. However, the ICD-10 has a diagnostic hierarchal system that may lead to an underassessment of comorbid disorders in the register. Information on psychiatric outpatient contacts of parents and siblings before 1995 was unavailable, and an underestimation of confounding by mental illness in the family is also possible. A potential overestimation of the results is also possible, if children born preterm or with low weight were more likely to have been referred to psychiatric departments owing to heightened awareness of their mental health. If the associations we found are true, undiagnosed children in the control group would tend to produce an underestimation of the reported risks.

Comparison with other studies

All previous studies on the association between gestational age and clinically verified ADHD were performed in very small samples of children with extremely low gestational ages at birth (below 28 completed weeks of gestation).[1–4] These studies also report an increased risk of ADHD compared with term controls.[1–4] A meta-analysis on cognitive and behavioural deficits in extremely premature infants support these findings.[5] However, the majority of preterm babies are born at higher gestational ages, and our findings may therefore have more important public health perspectives.

A serious limitation of previous studies on birth weight and the risk of ADHD is the lack of information on gestational age.[23–30] Some of the studies found an increased risk of ADHD among children with birth weights below 2500 grams,[23–26] but the apparent effect of birth weight was not separated from a potential effect of gestational age. However, other studies found that intrauterine growth may have an effect on long term learning, cognition, and attention.[6]

Possible explanations for the findings

Detailed knowledge of the mechanisms by which the fetal brain is affected by preterm birth and intrauterine growth retardation does not exist.[31]

In humans, repeated incidents of hypoxia and hypotension are common in premature children below 34 completed weeks of gestation.[32] Results from animal studies show that fetal hypoxia and hypotension may induce focal injury in the striatal complex of the basal ganglia,[33] with upregulation of the number of dopamine receptors.[34] This shared neurochemical abnormality for ADHD and injuries in preterm children is thought to be one of the explanations for an association between preterm delivery and ADHD in human,[35 36] and may also be one of several potential explanations in children with IUGR.

Morbidity and mortality are higher among preterm boys than among girls.[37] We were not able to detect any gender difference between the risks of the exposures under study and HKD. This could be because of the very small number of girls. Preliminary results indicate that the central dopamine system matures slower in males than in females, thereby increasing the period of vulnerability in the dopamine transmitter system.[38] This may partly explain the higher prevalence of boys with HKD and ADHD.[34]

What is already known on this topic

- Previous studies of very small samples have found that extreme premature delivery increases the risk of clinically verified ADHD
- No previous study has considered the association between proxy measures of intrauterine growth and the risk of clinically verified HKD or ADHD, but modest long term effects have been found on learning and attention

What this study adds

- Children with a history of preterm delivery, also close to term delivery, are at increased risk for clinically verified HKD or ADHD combined type
- Children born at term with low birth weights are also at increased risk for clinically verified HKD or ADHD combined type, and they have lower average birth weights adjusted for gestational age than controls

Because developing neurones are more vulnerable to cell death during the perinatal period,[39] biological and environmental insults associated with preterm birth[5] may promote some of the anatomical differences found among children with ADHD.[37] Unfortunately, we were not able to study these factors in detail.

Animal studies show that undernutrition in critical fetal periods during brain development may have long term effects on the brain, affecting attention, learning, and memory.[40] Our results support this hypothesis.

Since we have now shown an association between gestational age and birth weight and HKD, it could be interesting to investigate some of the complications more closely related to gestational age and birth weight. This, however, was beyond the scope of this paper. Further studies of mechanisms related to the delivery, causes of preterm delivery, and conditions affecting the child in the perinatal period are therefore needed.

Conclusions

Children born preterm, also close to term, or at 37 or more completed weeks of gestation with low birth weights (1500–2499 g) had an increased risk of clinically verified HKD.

Authors' affiliations

K M Linnet, K Wisborg, T B Henriksen, Perinatal Epidemiology Research Unit, Department of Obstetrics and Pediatrics, Aarhus University Hospital, Denmark
E Agerbo, National Centre for Register-Based Research, Aarhus University, Denmark
N J Secher, Department of Obstetrics and Gynaecology, Hvidovre Hospital, Copenhagen, Denmark
P H Thomsen, Psychiatric Hospital for Children and Adolescents, Aarhus University Hospital, Denmark

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IMAGES IN PAEDIATRICS

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Nonparalytic poliomyelitis in Lyme borreliosis

An 11 year old girl with a two week history of upper back pain presented with back stiffness and tenderness to palpation of the spinous processes. She had no sensory or motor abnormalities. Magnetic resonance imaging (MRI) showed no vertebral abnormalities, but unexpectedly swelling and vasogenic oedema of the spinal cord (fig 1), predominantly of the grey matter (fig 2), compatible with poliomyelitis. Cerebral spinal fluid (CSF) revealed lymphocytic pleocytosis (421 cells/µl, 99% lymphocytes), raised protein (1096 mg/l), and strongly increased (40-fold) intrathecal production of specific antibodies against *Borrelia burgdorferi*. Antibodies to enteroviruses could not be detected. Back pain, CSF, and MRI abnormalities resolved completely after a two week period of therapy with cefotaxime.

In neuroborreliosis, back pain results from meningoradiculoneuritis (Garin-Bujadoux-Bannwarth syndrome) and myelitis.[1] Lyme myelitis involves the white matter, resulting in paralysis. Nevertheless, in our patient Lyme borreliosis manifested as nonparalytic poliomyelitis, which itself is usually caused by enteroviruses.

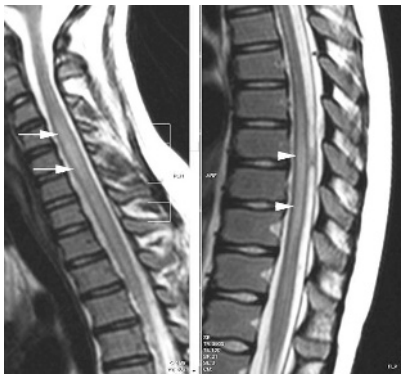

Figure 1 Sagittal T_2 weighted MRI of the spinal cord, showing a central high signal intensity extending with its maximum at the level of the lower cervical (arrows) and thoracic (arrowheads) spine.

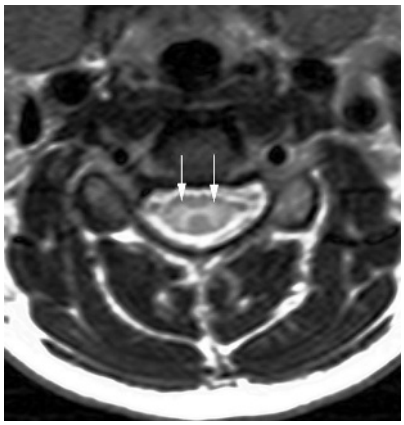

Figure 2 Axial T_2 weighted MRI of the spinal cord, showing a butterfly shaped high signal intensity of the grey matter (arrows).

A van Baalen, H Muhle, T Straube, O Jansen, U Stephani
University Medical Center Schleswig-Holstein, Christian-Albrechts-Universität zu Kiel, Germany; van.baalen@pedneuro.uni-kiel.de

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