Arnold-Chiari-II malformation and cognitive functioning in spina bifida

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Key words: cerebellum, cognition, Spina Bifida, neuropsychology
ABSTRACT

Objectives: Spina bifida is a multi-faceted neurological condition with a complex of neuropsychological sequelae. The cognitive outcome in spina bifida has frequently been attributed to the severity of the hydrocephalus. However, because of complex neuropathology the influence of hydrocephalus alone does not sufficiently explain the deficits in the cognitive profile in spina bifida. To date, little is known of the role of Arnold-Chiari-II malformation (ACM) in the cognitive profile of these patients. Aim of the present study is to delineate the specific contribution of the ACM in spina bifida by comparing children with ACM and those without ACM.

Methods: Fourty-six children between six and fifteen years of age underwent a neuropsychological assessment covering intelligence and a wide range of cognitive functions, like visuo-motor processing, attention, memory, word fluency, and speed of information processing. Comparisons were made between patients with ACM (ACM+) and without ACM (ACM-); all children with ACM+ also had hydrocephalus. Confounding effects of global cognitive impairment were eliminated, such that groups were matched on verbal IQ. Because of complex neuropathology, which is inherent to spina bifida the method applied was based on a comparison of cognitive profiles of the study group with profiles of patients with cerebellar damage and HC found in the literature.

Results: Children with ACM showed impaired visual analysis and synthesis, verbal memory, and verbal fluency, even after correction for global cognitive impairment.

Conclusion: The present data support the hypothesis that in addition to impairment in visual analysis and synthesis, which are related to both hydrocephalus and ACM, specific deficiencies in verbal memory and fluency may be attributed to ACM.

Abbreviations: SBH, spina bifida hydrocephalus; HC, hydrocephalus; ACM, Arnold-Chiari malformation; ACM +, patients with SB and ACM; ACM-, patients with SB but without ACM; WISC-III, Wechsler Intelligence Scale for Children 3d ed.; TIQ, total intelligence quotient; PIQ, performance intelligence quotient; VIQ, verbal intelligence quotient
Spina bifida is a heterogeneous congenital disorder with complex physical and neuropsychological symptomatology. It is associated with developmental anomalies of both the spine and the central nervous system. Different forms of spina bifida can be distinguished, varying from mild to severe. The most common form is myelomeningocele. Nearly all children with myelomeningocele develop a hydrocephalus (HC) and have Arnold-Chiari-II malformation (ACM). ACM involves a low tentorium insertion; herniation of the posterior fossa content; and beaking of the mesencephalic tectum.1

Due to improved diagnosis and treatment children with spina bifida and hydrocephalus (SBH) are more likely to have a total IQ within the normal range than in previous decades.2 3 Until now, the cognitive impairments in SB have frequently been attributed to the severity of the hydrocephalus and associated complications such as shunt revisions, infections or seizures.4 5 6 7 8 9 10 11 However, in SB, the conditions HC and ACM do not occur independently. Consequently, the influence of hydrocephalus alone can not sufficiently explain the deficits in the cognitive profile of these patients. Until now, little research has been conducted to the specific role of ACM. Some evidence suggests that ACM influences motor and cognitive development in SBH12. In particular, deficits in perceptual and motor timing13 and speech dysfluencies14 have been related to cerebellar dysmorphologies associated with spina bifida.

The purpose of the present study was explicitly acknowledge the specific contribution of the ACM in the cognitive profile of children with SB. Because of the complex neuropathological conditions of patients with SB mentioned above, the method applied was based on comparisons of cognitive profiles of our study-group with profiles of patients with cerebellar damage and HC found in the literature. Our premise is that tasks which rely on cognitive functions such as automation, verbal fluency and visual processing are subserved by cerebellar structures, and thus could be disrupted in SBH due to cerebellar malformation. For this, a complete neuropsychological test battery, including tests for cerebellar cognitive functions was administered to two groups of children with SB, those without ACM (ACM-) and those with ACM (ACM+).
METHOD

Study group
The study group was selected, using the following inclusion criteria: 1) born with spina bifida in our hospital or admitted for surgery later on; 2) date of birth between 01-01-1988 and 31-12-1997; 3) T1-weighted Magnetic Resonance Images (MRI) conclusive for absence or presence of ACM. The diagnosis of this condition was based on MRI criteria defined by Stevenson (2004). Seven-eight children fulfilled these inclusion criteria. For various reasons (refusal to participate, foreign language, profound retardation precluding formal testing), 32 of the 78 selected cases could not be adequately examined. Thus, the final study group consisted of 46 individuals. All children underwent spinal surgery within 5 years after birth.

To assess the effect of ACM, subgroups of children without (ACM-) and with ACM (ACM+) were formed. Furthermore, nonretarded ACM- and ACM+ groups were selected on the basis of a verbal IQ of 75 or above on the Wechsler-Intelligence Scale-III (WISC-III). In this way, the possible confounding effects of global cognitive impairment were eliminated.

At the time of assessment children were between six and fifteen years of age. Mean age and age range of the subgroups are presented in table 1a.

The experimental procedures of this study were approved by the Committee on Research Involving Human Subjects (CMO Regio Arnhem–Nijmegen) of the Radboud University Nijmegen Medical Centre. Written consent was obtained from the parents of each subject.

Procedure
All children underwent an individual neuropsychological assessment, for most children in two assessment sessions. The order of the neuropsychological tests was fixed. The total duration of the psychological assessment varied between 3.5 and 5 hours.

Measures
The neuropsychological assessment intended to cover the following cognitive functions: intelligence, visual analysis and synthesis, visuo-motor functioning, (non)verbal memory, processing speed, verbal skills, and verbal fluency. Subtests of three different test batteries were used (Wechsler-Intelligence Test, WISC-III; Kaufman-ABC, K-ABC; and Revised Amsterdam Kinder Intelligentie Test, RAKIT) plus Stroop-Color-Word-Test, Bourdon-Vos Concentration Test, Beery’s Visuomotor Integration (VMI), and 15-Words-Test. For the Stroop-Color-Word-Test, the subtests of the RAKIT and the 15-Words-Test, the oldest children passed the limits of the age norm. In these cases the highest age norms were applied.

Statistical analysis
Statistical analyses were performed using SPSS 12.0.1 for Windows. ANOVAs were used to examine the differences in ACM- and ACM+ concerning verbal and performance intelligence (VIQ and PIQ), and also the discrepancy among both (VIQ-PIQ). MANOVAs were conducted with the different subtests per cognitive functions as dependent variables and group (ACM- versus ACM+) as independent variable. The same analyses were then performed for the nonretarded groups (VIQ≥75 ACM-versus VIQ≥75 ACM+). Significance was considered for each of the ANOVAs when
p< 0.05. Because of the large number of comparisons in MANOVAs, the alpha significance level .05 was adjusted using the Bonferroni correction.
RESULTS
Cognitive outcome
In the complete group the factor ACM was significant: ACM+ children had a lower VIQ (see also scatterplot fig 1 and table 1a) and TIQ than ACM- children. In the nonretarded group these differences were smaller and did only reach statistical significance for PIQ and TIQ. In this nonretarded group, ACM+ and ACM- children matched well on VIQ. Overall, discrepancies between VIQ and PIQ were significant for both the complete and the nonretarded group.

[insert fig 1; Legenda fig 1: Scatterplot of individual VIQ and PIQ scores per group. Uninterrupted lines indicate the mean VIQ (horizontal line) and mean PIQ (vertical line) for the ACM+ group. Dotted lines display mean VIQ and PIQ of the ACM- group.]
Table 1a: Mean scores (stdev) of cognitive outcome

<table>
<thead>
<tr>
<th></th>
<th>AllACM-</th>
<th>AllACM+</th>
<th>F</th>
<th>sign.</th>
<th>VIQ≥75ACM-</th>
<th>VIQ≥75ACM+</th>
<th>F</th>
<th>sign.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ages (Age range)</td>
<td>10;0 (6;6-14;11)</td>
<td>10;3 (6;4-15;1)</td>
<td>9;7 (6;6-14;11)</td>
<td>9;8 (6;4-12;9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VIQ</td>
<td>95.8 (15.3)</td>
<td>80.3 (17.4)</td>
<td><strong>F(1,44)= 9.9</strong></td>
<td><strong>.003</strong></td>
<td>98.9 (12.9)</td>
<td>91.3 (9.1)</td>
<td><strong>F(1,32)= 4.0</strong></td>
<td><strong>.055</strong></td>
</tr>
<tr>
<td>PIQ</td>
<td>94.2 (16.0)</td>
<td>68.2 (16.5)</td>
<td><strong>F(1,44)= 28.5</strong></td>
<td><strong>.000</strong></td>
<td>97.5 (13.3)</td>
<td>77.7 (11.9)</td>
<td><strong>F(1,32)= 20.9</strong></td>
<td><strong>.000</strong></td>
</tr>
<tr>
<td>TIQ</td>
<td>94.5 (15.8)</td>
<td>72.6 (16.6)</td>
<td><strong>F(1,44)= 20.2</strong></td>
<td><strong>.000</strong></td>
<td>97.9 (12.7)</td>
<td>83.5 (8.2)</td>
<td><strong>F(1,32)= 15.5</strong></td>
<td><strong>.000</strong></td>
</tr>
<tr>
<td>VIQ-PIQ</td>
<td>1.6 (13.1)</td>
<td>12.1 (11.14)</td>
<td><strong>F(1,44)= 8.5</strong></td>
<td><strong>.006</strong></td>
<td>1.47 (13.9)</td>
<td>13.6 (12.5)</td>
<td><strong>F(1,32)= 7.2</strong></td>
<td><strong>.012</strong></td>
</tr>
</tbody>
</table>

Note. A significance level of p<.05 was used.
Table 1b: Mean scores (stdev) of cognitive profile and results of the multivariate analyses of variance

<table>
<thead>
<tr>
<th>Test Battery</th>
<th>VIQ\textsubscript{75 ACM−} n</th>
<th>VIQ\textsubscript{75 ACM+} n</th>
<th>F</th>
<th>sign.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Visual analysis and synthesis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Picture completion</td>
<td>WISC-III 10.7 (2.6)</td>
<td>8.4 (2.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Object assembly</td>
<td>WISC-III 9.2 (2.8)</td>
<td>5.9 (3.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Picture arrangement</td>
<td>WISC-III 9.8 (2.2)</td>
<td>5.8 (2.1)</td>
<td>F(5,28)=6.59  .000</td>
<td></td>
</tr>
<tr>
<td>Block design</td>
<td>WISC-III 9.5 (2.7)</td>
<td>7.5 (2.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestalt closure</td>
<td>K-ABC 10.1 (2.5)</td>
<td>8.4 (3.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Visuo-motor function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mazes</td>
<td>WISC-III 10.0 (2.1)</td>
<td>7.8 (3.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VMI ss</td>
<td>Beery 98.9 (8.7)</td>
<td>90.1 (8.3)</td>
<td>F(3,25)=4.43  .012</td>
<td></td>
</tr>
<tr>
<td>Discs</td>
<td>RAKIT 15.9 (5.3)</td>
<td>10.5 (5.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Verbal memory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15WordTest total</td>
<td>----- 46.2 (9.6)</td>
<td>34.1 (12.7)</td>
<td>F(4,28)=5.67  .002</td>
<td></td>
</tr>
<tr>
<td>15WordTest recall</td>
<td>----- 10.1 (2.8)</td>
<td>6.1 (3.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Word order</td>
<td>K-ABC 10.5 (2.2)</td>
<td>7.8 (3.0)</td>
<td></td>
<td></td>
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<tr>
<td>Digit Span</td>
<td>WISC-III 10.4 (2.4)</td>
<td>8.6 (2.0)</td>
<td></td>
<td></td>
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<tr>
<td><strong>Nonverbal memory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand movements</td>
<td>K-ABC 10.4 (2.2)</td>
<td>9.8 (2.6)</td>
<td>F(2,31)=1.12  .34</td>
<td></td>
</tr>
<tr>
<td>Spatial memory</td>
<td>K-ABC 9.8 (2.6)</td>
<td>8.4 (2.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Processing speed</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coding</td>
<td>WISC-III 9.2 (2.2)</td>
<td>6.5 (3.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symbol search</td>
<td>WISC-III 10.5 (2.8)</td>
<td>7.4 (3.3)</td>
<td>F(4,20)=1.73  .182</td>
<td></td>
</tr>
<tr>
<td>Stroop_color\textsuperscript{1}</td>
<td>----- 89.1 (22.0)</td>
<td>99.0 (22.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BourdonRT_tot\textsuperscript{1}</td>
<td>----- 19.9 (5.2)</td>
<td>21.7 (6.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Verbal skills</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Similarities</td>
<td>WISC-III 10.4 (2.8)</td>
<td>8.3 (2.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comprehension</td>
<td>WISC-III 9.5 (1.7)</td>
<td>8.1 (2.2)</td>
<td>F(4,29)=1.82  .152</td>
<td></td>
</tr>
<tr>
<td>Vocabulary</td>
<td>WISC-III 10.1 (2.9)</td>
<td>8.9 (1.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arithmetics</td>
<td>WISC-III 9.7 (2.4)</td>
<td>8.4 (3.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Verbal Fluency</strong></td>
<td>RAKIT 14.2 (4.7)</td>
<td>8.5 (4.4)</td>
<td>F(1,32)=12.8  .001</td>
<td></td>
</tr>
</tbody>
</table>

Notes.
A significance level of p<.05 was adjusted using Bonferroni correction.
\textsuperscript{1}: Score represents time to perform, so high scores indicates poor (slow) performance.
Cognitive profile
In the complete group, ACM+ children (AllACM+) were significantly impaired on all tests as compared ACM- children (AllACM-) due to global cognitive impairment. Therefore, to assess differences in cognitive profile, we focused on a comparison of the non-retarded ACM- versus ACM+ group (VIQ\textgreater=75ACM- versus VIQ\textgreater=75ACM+).

The MANOVAs indicated significant main effects for visual analysis and synthesis, verbal memory, and verbal fluency.

Mean scores, standard deviations and p-values of MANOVAs are reported in table 1b.
DISCUSSION

Aim of the current study was to delineate the specific influence of ACM in the cognitive profile of spina bifida patients. Results revealed that ACM+ patients had a significantly lower PIQ than ACM- patients, even after eliminating the confounding effect of global cognitive impairment. In the nonretarded group the patients with and without ACM matched well on VIQ, which is not supposed to be associated with cerebellar dysfunction.

In terms of cognitive profile, the ACM+ group performed particular poorly on tests requiring visual analysis and synthesis, verbal memory, and verbal fluency. Since all ACM+ patients also had hydrocephalus, which is inherent to myelomeningocele, it remains difficult to separate out the influences of HC and ACM on cognitive impairment. However, two methods were applied to delineate the specific effect of the ACM. First, the confounding effect of hydrocephalus was reduced by selecting nonretarded ACM- and ACM+ groups matched on VIQ, leaving those patients who had a mild or well treated hydrocephalus. Second, the specific characteristics of the cognitive profile were compared to the neuropsychological literature on cerebellar disorders and HC.

Recently, evidence has been presented that the cerebellum is part of a cerebrocerebellar network and contributes not only to motor processes, but also to cognitive functions. The present study suggests the role of the cerebellum in both motor speed and coordination as well as higher cognitive functioning in patients with spina bifida. The nonretarded ACM+ group showed impaired visual analysis and synthesis. On the one hand, in consideration of the aspects of visuo-motor integration of the tasks, low performances could be attributed to HC. On the other hand, poor performances on these tasks could -in addition to HC- reflect reduced processing speed and poor visual-spatial function related to cerebellar malformation.

Furthermore, results revealed deficits in verbal memory and fluency among ACM+ patients. This finding is consistent with the pattern of cognitive impairment reported in subjects with cerebellar damage. Although deficits in verbal memory and verbal fluency have also been related to HC in earlier studies, most of those studies are limited by a selection bias (inclusion of HC patients of heterogeneous etiologies, or SB of diverging severity) or by an underestimation of the confounding influence of the ACM. Given the co-occurrence of HC and ACM in patients with SB, we conclude that the deficits in verbal memory and fluency must most likely be ascribed to the cerebellar malformation.

To conclude, the current data support the hypothesis that HC alone is not a sufficient explanation of the cognitive deficits in spina bifida. It seems that impaired visual analysis and synthesis are related to both HC and ACM, whereas deficiencies in verbal memory and fluency may be attributed to ACM. Since spina bifida is associated with complex neuropathology, further disentangling the contribution of the different additional malformations requires studies correlating anatomical neuroimaging data with cognitive measures.

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Dept of Epidemiology and Biostatistics (N. Roeleveld PhD MSc)

Radboud University Nijmegen:
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Figure 1: Scatterplot VIQ-PIQ nonretarded ACM- versus ACM+ group

Fig 1: Scatterplot of individual VIQ and PIQ scores per group. Uninterrupted lines indicate the mean VIQ (horizontal line) and mean PIQ (vertical line) for the ACM+ group. Dotted lines display mean VIQ and PIQ of the ACM- group.
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