





# Brain malformations and cognitive performance in spina bifida

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## PUBLICATION DATA

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## ABBREVIATIONS

|         |  |
|---------|--|
| CBA     | Clivus-base angle  |
| KABC    | Kaufman Assessment Battery for Children                  |
| SBA     | Spina bifida aperta                                      |
| SBO     | Spina bifida occulta                                     |
| TBA     | Tentorium-base angle                                     |
| TKA     | Tentorium-kink angle                                     |
| WAIS-IV | Wechsler Adult Intelligence Scale, Fourth Edition        |
| WISC-IV | Wechsler Intelligence Scale for Children, Fourth Edition |

**AIM** To systematically characterize radiological features of patients with spina bifida, their relationship to cognitive function, and differences between spina bifida aperta (SBA) and spina bifida occulta (SBO).

**METHOD** In a retrospective study of 265 patients (117 females, 148 males; median age at imaging 11y, range 1–47y; SBA  $n=206$ , SBO  $n=59$ ), the radiological phenotype was assessed through magnetic resonance imaging (MRI) (SBA  $n=171$ , SBO  $n=59$ ). In 126 patients (SBA  $n=116$ , SBO  $n=10$ ) Kaufman Assessment Battery for Children (KABC) or Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV) and Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV) were performed.

**RESULTS** Patients with spina bifida show numerous brain malformations, always present for SBA but rarely for SBO. The most frequent brain malformations in SBA included abnormal corpus callosum (69%), hypoplastic pons (50%), and hypoplastic mesencephalon (20%). Cognitive total IQ scores were below average in 44% (KABC) to 49% (WISC-IV) of children with SBA, while almost all children with SBO scored at least average. Stenogyria ( $p=0.006$ ), pons ( $p=0.003$ ), and mesencephalon hypoplasia ( $p=0.01$ ) correlated with lower total IQ score and verbal comprehension. Various brain malformations correlate significantly with several cognitive domains, while lesion level only correlates with processing speed.

**INTERPRETATION** IQ scores were significantly lower in patients with SBA than in patients with SBO. Verbal competence, perceptual reasoning, and working memory were significantly impaired for SBA and correlated with stenogyria and abnormalities of the midbrain and corpus callosum.

Spina bifida is the most frequent non-lethal birth defect of the central nervous system with an incidence of 0.5 to 2 per 10 000 established pregnancies, including live births, pregnancy losses, and abortions.<sup>1</sup> Spina bifida originates during embryogenesis and results from failure of the neural tube to close between the 18th and 28th embryonic day. The latter results in defects of the vertebral arches, with or without affecting the spinal cord.<sup>2</sup> Though the reason is still not clear, a multifactorial genesis is proposed, including genetic predisposition, environmental factors, and maternal conditions.<sup>3</sup> Spina bifida occurs in various grades of severity and can be classified in two main groups: spina bifida aperta (SBA), the open form, and spina bifida occulta (SBO), the closed form. In the case of the more severe form, SBA, the defect is not covered by skin. The spectrum of clinical symptoms depends on the level and the extent of the damaged area and ranges from no or minimal impairment to severe neurological symptoms such as motor and sensory disabilities, bladder and bowel dysfunction,

and orthopaedic problems such as foot deformities, contractures, and scoliosis.

Disturbances of neural tube closure can result in an altered pattern of programmed fetal development and subsequent anatomical brain and spinal malformations. Approximately 85% of patients with SBA develop hydrocephalus and have a Chiari malformation, resulting in the necessity to implant a cerebrospinal fluid drain.<sup>4</sup> Nearly all patients with SBA have complex patterns of partial agenesis or hypoplasia but not total agenesis of the corpus callosum architecture.<sup>5</sup> Moreover, abnormalities of the cerebellum<sup>6</sup> and fossa posterior<sup>7</sup> have been reported.

Patients with SBA show a lower IQ compared to age-matched peers, most noticeably in performance IQ rather than in verbal IQ.<sup>8</sup> In this respect, the lower volume of the posterior regions of the corpus callosum in patients with SBA correlates with a reduction in IQ.<sup>5</sup> Hydrocephalus and Chiari malformation alone are not sufficient to explain the cognitive deficits in spina bifida.<sup>9</sup> It has been suggested

that structural brain abnormalities are more important determinants of cognitive outcome than shunt malfunction.<sup>10</sup> To our knowledge, there are no data comparing cognition between SBA and SBO. We expected better cognitive function in SBO because in clinical practice fewer associated brain malformations are described within those patients. The aim of this study was to systematically characterize radiological features of patients with spina bifida and to investigate the relationship between cognitive functions and various brain malformations between SBA and SBO.

## METHOD

A retrospective study was performed on a cohort of 265 patients with spina bifida (SBA  $n=206$ , SBO  $n=59$ ) treated at the Center for Chronically Sick Children, Charité University Medicine, Berlin from 1990 to 2018. The median age of patients was 11 years (range 1–47y) at the time of imaging (Table S1, online supporting information). All adult patients had been treated at the centre since childhood. The study was approved by the local ethics committee (approval no. EA2/070/15). We reviewed medical records of all patients and collected data on medical history, clinical, and radiological findings in a database with standardized variables. Cranial magnetic resonance imaging (MRI) with a balanced state of the liquor drainage was chosen for the analysis in patients with drained hydrocephalus. Those patients had to have no shunt revision at least within 1 year after cognition testing. For the evaluation of spinal MRI, the T1 and T2 sequences had to be available to determine whether a spinal lipoma was present or not. In our study, SBA was defined as a spinal dysraphism not covered by skin. The spinal dysraphism in SBO had to be covered by skin. We note that SBA is often used synonymously to myelomeningocele and SBO synonymously to other spinal malformations. However, this association is not always valid. The patients were furthermore discriminated by the anatomical lesion level. To study the influence of age on the metric of the posterior fossa, we recruited an age-matched control group of 130 patients from the Department of Pediatric Neurology, who had received a routine cranial MRI examination as part of the diagnostic work-up for, for example, headache, psychosomatic disorder, febrile seizure. These images had undergone radiological evaluation by a paediatric neuroradiologist and had been rated as showing normal central nervous system morphology. In order to investigate the impact of age on the morphometry of the posterior fossa, the patients and controls were age-matched.

## MRI

Cranial MRI acquisitions were performed at the Departments of Pediatric Radiology and Pediatric Neuroradiology, and included axial, sagittal, and coronal T1- and T2-weighted sequences (Siemens Magnetom-Avanto/Symphony/Aera, 1.5-Tesla, Erlangen, Germany). In unclear cases concerning the presence of residual parts of corpus

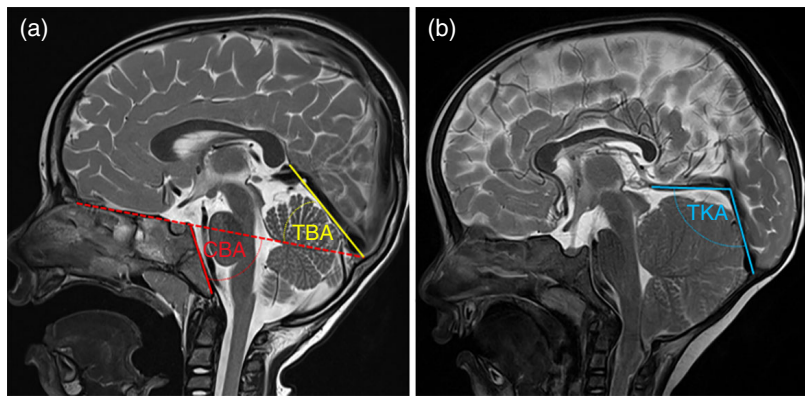
## What this paper adds

- Brain malformations occur more frequently in spina bifida aperta (SBA) than in spina bifida occulta (SBO).
- Cognitive impairment is less frequent in SBO.
- Hydrocephalus, stenogryria, midbrain, and corpus callosum abnormalities are associated with lower cognitive function.
- Difference in prognosis in SBO versus SBA can alter prenatal counselling.

callosum, diffusion tensor images were evaluated. Detailed image reevaluation was performed for each patient by a paediatric neuroradiologist. The size of the midbrain and pons was analysed according to Hashimoto et al.<sup>11</sup> The clivus-base angle (CBA), tentorium-base angle (TBA), and tentorium-kink angle (TKA) were measured on mid-sagittal slices using two lines (Fig. 1): (1) to determine the CBA, the first line was placed along the postero-superior surface of the clivus connecting the cranial part of the clivus and the anterior border of the foramen magnum; (2) the second line was placed along the superior surface of the skull base. The angle at which both lines crossed represents the CBA (Fig. 1a). To measure the TBA, the first line was positioned along the tentorium between cerebellum and the occipital lobe, the second line was the same as in CBA. The angle between the lines represents the TBA (Fig. 1a). The angle resulting from a kink within the tentorium (Fig. 1b) was defined as TKA. All anatomical structures needed to measure the angles could be easily identified by MRI.

## Cognitive test

Cognitive tests were offered for all children before school enrolment. Not all parents decided to have their children undergo this diagnostic procedure. The mental processing composite from the Kaufman Assessment Battery for Children (KABC) of 76 patients with spina bifida at a median age of 6 years (range 5–11y) was used to operationalize the general cognitive ability of a child as an important predictor of academic outcome. The mental processing composite is an age-related standard scale score (mean=100; standard deviation=15) of the two indices sequential and simultaneous processing. Furthermore, we used the German adaption of the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV) and equivalent test for adults, the Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV), in 50 patients with spina bifida at a median age of 11 years (range for WISC-IV: 7y–16y 10mo; for WAIS-IV: 20y 1mo–20y 11mo). The test consists of one global index (full scale IQ) and four composite scores: verbal competence, perceptual reasoning, working memory, and processing speed. The indices of the WISC-IV are age-related (standard scale score/IQ scale: mean=100, standard deviation=15). Children between 3 and 12 years of age can be tested with KABC, while WISC-IV is suited for children between 6 and 16 years. In contrast to WISC-IV, KABC is a test less language-oriented and thus better suited for preschool children. Subtests in these two tests cannot be compared and have different performance ranges.



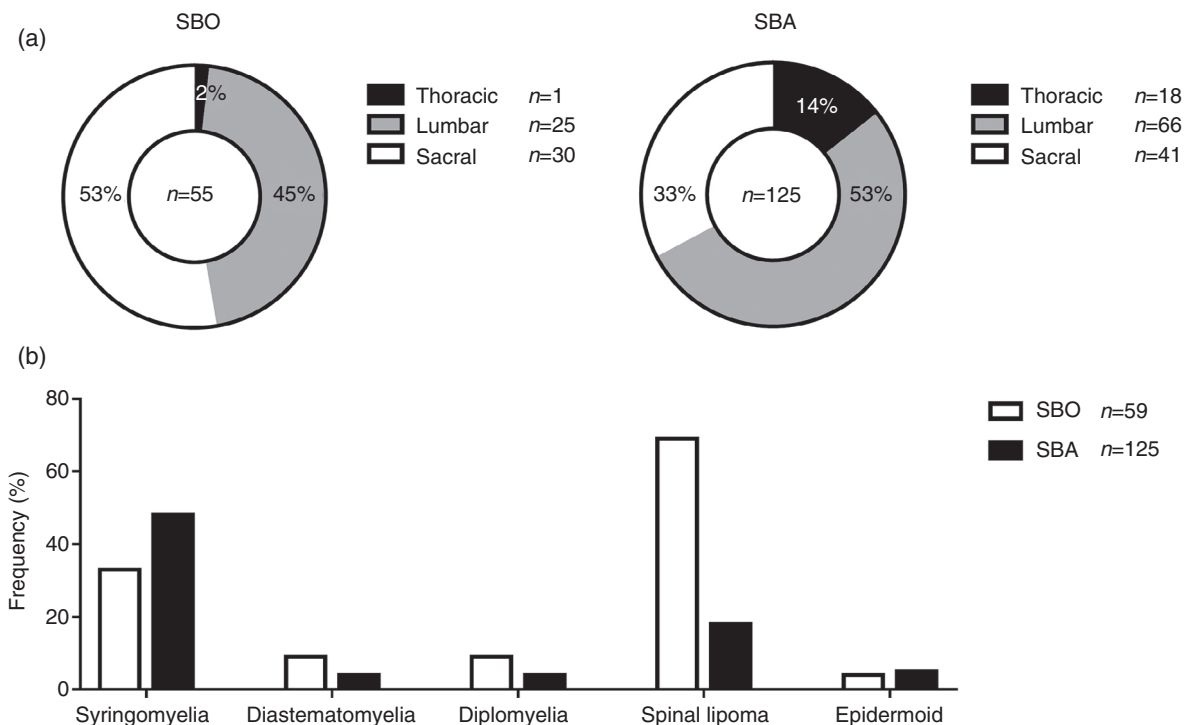
**Figure 1:** Cranial magnetic resonance imaging (MRI)-based measurement of the clivus-base, tentorium-base, and tentorium-knick angles (TKAs), illustrating the measurement method. (a) Sagittal T2-weighted cranial MRI from control patient showing how the clivus-base angle (CBA) and tentorium-base angle (TBA) were determined. The continuous red line was positioned along the posterior surface of the clivus, the dashed red line along the superior surface of the skull base, and the yellow line along the tentorium between cerebellum and the occipital lobe. (b) Sagittal T2-weighted cranial MRI from patient with spina bifida aperta. [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

In seven patients with SBA it was impossible to conduct the tests, as they had no understanding of instruction because of their intellectual disability. These patients were excluded from the analysis. All tests were carried out by an experienced certified psychologist.

For most groups the number of cases was too small to test for a normal distribution. Therefore, we used the more conservative Mann–Whitney *U* test to compare the distribution of IQ values.

### Statistical analysis

Statistical analysis and graph design were performed using SPSS Statistics Version 25 (IBM Corp., Armonk, NY, USA) and GraphPad Prism (version 6.04 for Windows, GraphPad Software, La Jolla California, USA) respectively. To characterize frequency distributions, we carried out univariate analyses. To evaluate the correlation of nominal and ordinal-scaled variables, we used Fisher's exact test. Median comparisons were tested using Welch's *t*-test for



**Figure 2:** Spinal malformations in patients with spina bifida. (a) The anatomic lesion level is lower in patients with spina bifida occulta (SBO) than in spina bifida aperta (SBA).  $\chi^2$  test,  $p=0.007$ . (b) Frequency of various spinal malformation in patients with SBA and SBO.

normal distributed samples and Mann–Whitney *U* test for parameters without normal distribution. Spearman's rank correlation coefficient was used to analyse the relationship between two variables. A *p*-value equal to or below 0.05 was considered statistically significant. Data are displayed as mean±standard error of the mean.

## RESULTS

Our cohort included 265 patients with spina bifida with a well-balanced sex distribution (117 females [44%], 148 males [56%]): 74% (*n*=206) with SBA and 36% (*n*=59) with SBO. Half the patients had a lumbar anatomic lesion level, followed by 39% sacral and 11% thoracic lesion levels. Finally, 188 cranial MRI (*n*=157 SBA, *n*=31 SBO) and 184 spinal MRI (*n*=125 SBA, *n*=59 SBO) were analysed (Fig. S1, online supporting information).

### Spinal abnormalities

In a first step, we reassessed the radiologically defined anatomic lesion levels, distinguishing for further statistical analysis between sacral, lumbar, and thoracic lesions. These lesion levels were found to be significantly lower in patients with SBO (53% had sacral lesions) than in patients with SBA (52% had lumbar lesions) (Fig. 2a). In patients with SBA, 96% had a myelomeningocele and only about 1% a meningocele. Patients with SBO, on the other hand, showed mostly different types and combinations of tethered cord and intraspinal lipoma (Table S2, online supporting information). Other spinal abnormalities such as syringomyelia, diastematomyelia and diplomyelia, intraspinal lipoma and epidermoid, and meningomyelocele occur in both patient groups (Fig. 2b). No significant relations between lesion level and spinal abnormalities were found (Table S3, online supporting information).

### Brain abnormalities

Cerebral anomalies showed a striking difference between patients with SBA and those with SBO. Patients with SBO hardly exhibited cerebral malformations while all patients with SBA displayed cerebral anomalies with some of them having an impact on the therapeutic treatment (i.e. shunt placement). As an example, 92% of patients with SBA but only 6% of patients with SBO had a hydrocephalus that

needed a shunt in 99% of the cases. Similarly, a Chiari malformation, hypoplastic pons, and mesencephalon were found to be much more prevalent in patients with SBA (Fig. 3a). In addition, the extent of the Chiari malformation, measured by the extent of cerebellar tonsil herniation, was much more severe in patients with SBA compared to patients with SBO (Fig. 3b). Similarly, medullary kinking was only observed in patients who also exhibited a Chiari malformation. Significant correlations were found between lesion levels and hypoplasia of the pons and mesencephalon, as well as between pons hypoplasia and the extent of the cerebellar tonsil herniation (Table S3).

In addition to the quantification of the cerebral abnormalities described above, certain areas of the brain crucial for its function were also analysed in a more descriptive way. In certain cases, however, this led to ambiguities regarding the interpretation of the MRI. For example, the tectum (Fig. 3c) was in some cases neither normal nor did it display the classic beaking deformation but instead yielded various deformation patterns on MRI (examples shown in Fig. 3d,e,f). While a complete corpus callosum agenesis did not occur, specific subregions of the corpus callosum were absent or hypoplastic. The splenium (54%) and the truncus (45%) were affected most frequently, less prevalent were abnormalities of the rostrum (28%) or genu (23%) (Fig. 3g). The typical combinatorial variants of hypoplastic corpus callosum and agenesis are listed in Figure 3g.

### Magnetic resonance-based morphometry of the posterior fossa

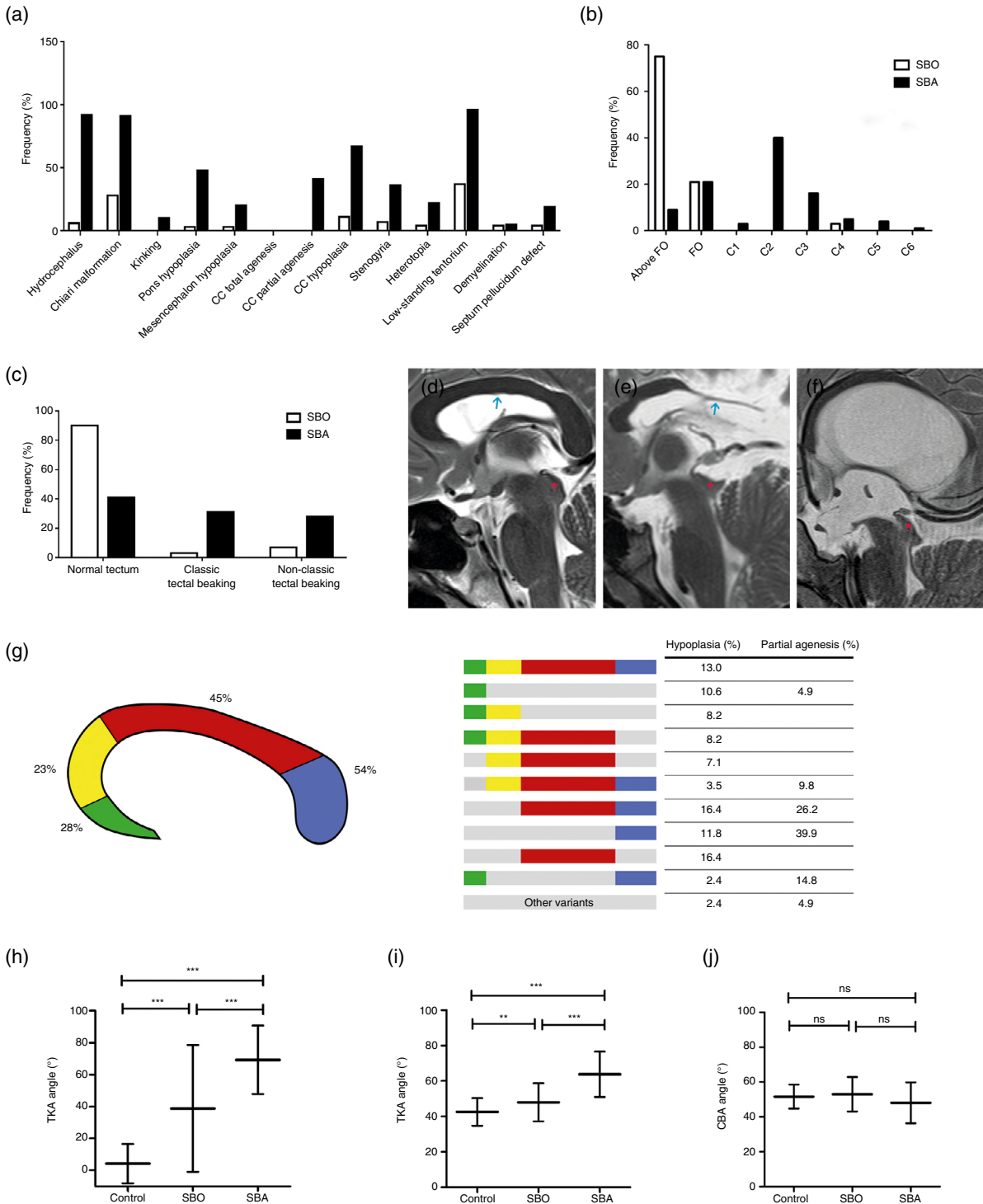
For a description of the posterior fossa we used the morphometric parameters CBA, TBA, and TKA, as delineated in the 'Method' section. The standard values were calculated based on the control group. The distribution of the values of posterior fossa metrics showed no correlation to the age (CBA:  $r=0.110$ ,  $p=0.21$ ; TBA:  $r=-0.009$ ,  $p=0.92$ ; TKA:  $r=-0.162$ ,  $p=0.07$ , Spearman's rank correlation coefficient). TBA and TKA were significantly different in controls, SBO, and SBA. This was not the case for CBA (Fig. 3h,i,j; Table S4, online supporting information). None of the morphometric parameters correlated with the lesion level and the extent of cerebellar herniation.

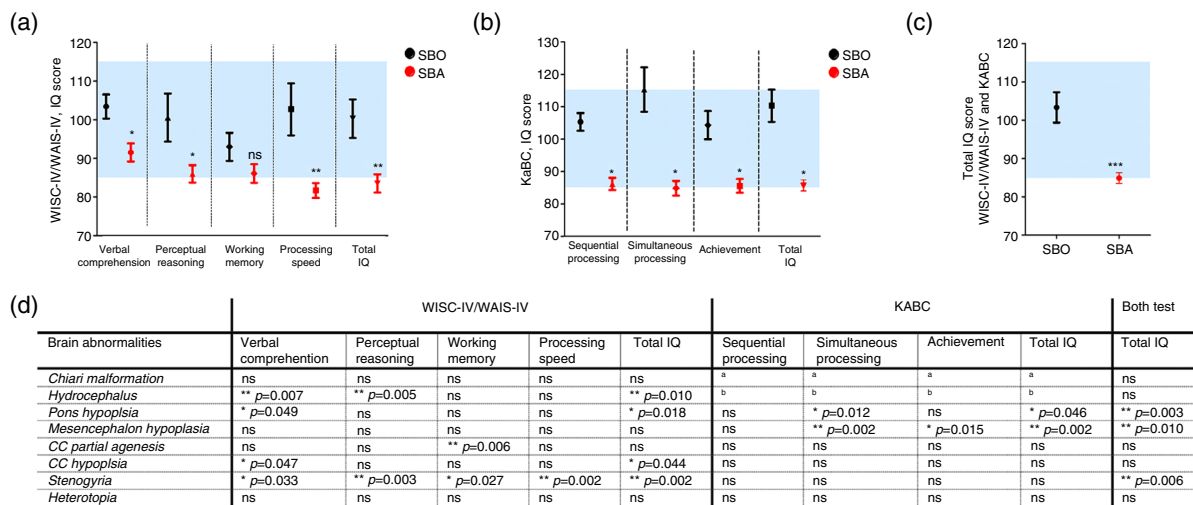
**Figure 3:** [Displayed on the following page] Brain malformations in patients with spina bifida. (a) Frequency of various spinal malformation in patients with spina bifida aperta (SBA; black columns) or spina bifida occulta (SBO; white columns). (b) Extent of cerebellar tonsil herniation in patients with SBA or SBO. FO, foramen magnum; C1–6, cervical spine level. (c) Frequency of tectum beaking in patients with SBA or SBO. (d) Sagittal T2-weighted cranial MRI from control patient showing normal formation of tectum (red star) and normal corpus callosum (blue arrow). (e) Cranial MRI scans from patient with SBA showing non-classic tectum beaking (red star) (i.e. inferior displacement of tectum from colliculi) and hypoplastic truncus and splenium of corpus callosum (blue arrow), and (f) classic tectum beaking (red star) (i.e. superior displacement of tectum). (g) Corpus callosum (CC) subregions affected by hypoplasia and/or partial agenesis (rostrum in green, genu in yellow, truncus in red, splenium in blue). The table on the right gives the frequency of occurrence of various CC abnormalities. Colour bars represent the affected CC subregion (hypoplasia and/or agenesis) and grey a normal formation of specific part of CC. (h,i,j) Morphometry of the posterior fossa. The mean and standard deviation (±1SD) are given for the (h) tentorium-kink angle (TKA), (i) tentorium-base angle (TBA), and (j) tentorium-kink angle (CBA) in patients with SBA and SBO as well as in a control group (control *n*=104, SBA *n*=157, SBO *n*=31; TBA and CBA values normally distributed [Welch's *t*-test]; TKA values without normal distribution [Mann–Whitney *U* test]). \*\**p*<0.01, \*\*\**p*<0.001; ns, no significance.

## Cognitive profile

The total IQ scores were below average (i.e. below 85 points) in almost half of the patients with SBA (in 44% tested using KABC and 49% using WISC-IV/WAIS-IV). The same was true for only one patient with SBO tested by WISC-IV/WAIS-IV. This patient was the only one within the SBO group showing various brain malformations (shunted hydrocephalus, chiari malformation, hypoplastic pons, and mesencephalon) and had a primary tethered cord with an atrophic spinal cord. Since in the

SBO group only one patient showed brain malformation and cognitive deficits, we analysed only patients with SBA to investigate the relationship between cognitive functions and various brain malformations. The performance levels of almost all cognitive domains in WISC-IV/WAIS-IV (verbal comprehension  $p=0.037$ , perceptual reasoning  $p=0.024$ , processing speed  $p=0.003$ , and total IQ  $p=0.007$ ) and all domains in KABC (sequential processing  $p=0.038$ , simultaneous processing  $p=0.014$ , achievement  $p=0.047$ , total IQ  $p=0.011$ ) differed significantly between patients





<sup>a</sup>only 2 spina bifida patients from  $n=45$  without chiari malformation  
<sup>b</sup>only 1 spina bifida patients from  $n=45$  without hydrocephalus

**Figure 4:** Cognition profile of patients with spina bifida. Cognitive performance of patients with spina bifida aperta (SBA) and occulta (SBO) measured using the (a) Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV)/Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV) test (SBA  $n=43$ , SBO  $n=7$ ) and (b) Kaufman Assessment Battery for Children (KABC) test (SBA  $n=73$ , SBO  $n=3$ ). (c) Comparison of total IQ score between patients with SBA and SBO considered with both test together (SBA  $n=116$ , SBO  $n=10$ ). The blue field shows the range of average cognitive score in the average population. Data shown as mean  $\pm$  standard error of the mean. (d) Relation of brain abnormalities to the cognitive score of WISC-IV/WAIS-IV and KABC. For all graphs: Mann–Whitney  $U$  test. \* $p<0.05$ , \*\* $p<0.01$ , \*\*\* $p<0.001$ ; ns, no significance. [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

with SBO and SBA. Patients with SBA had problems particularly in the domain ‘processing speed’ (Fig. 4a,b,c). This was the only domain correlated with the lesion level ( $p=0.04$ ; Table S5, online supporting information).

We detected significant differences across several cognitive domains based on the presence of stenogyria, midbrain abnormalities, hydrocephalus, and corpus callosum abnormalities (Fig. 4d). This suggests that these brain abnormalities may have the greatest impact on the cognitive performance of patients with SBA.

## DISCUSSION

In this study we systematically characterized radiological features of patients with spina bifida and correlated their cognitive function with brain malformations. We showed that all patients with SBA had brain malformation whereas only one patient with SBO in our cohort of 265 patients exhibited multiple abnormalities in brain imaging. Previous reports did not explicitly distinguish between the entities SBA and SBO.<sup>4,5</sup> However, our results highlighted the importance of such a discrimination when counselling families, not only for associated malformations but also regarding the prognosis of an affected child. This knowledge is of high importance for early prenatal ultrasound-based diagnosis that is based on signs indicative of a Chiari malformation<sup>12</sup> starting from the 11th to 14th weeks of gestation rather than signs of fetal spine abnormalities. Our study showed that patients with SBO rarely exhibit a Chiari malformation. It is therefore easily comprehensible that prenatal detection rates are low with about 7% in

individuals with SBO<sup>13</sup> and much higher with an average of 68% (range 33–100%) in patients with SBA.<sup>14</sup> Thus, the visualization of the anomaly of the fetal spine and identification of indicator signs in the first or second trimester may increase the detection rate of SBO.

Malformations of the brain in patients with SBA include hydrocephalus, Chiari malformation, pons and mesencephalon hypoplasia, corpus callosum malformations, stenogyria, heterotopia, demyelination, and septum pellucidum defect. The cognitive impairment in patients with SBA is significantly more frequent than in population norms.<sup>15,16</sup> In our centre we offer cognitive testing to all families. Decisions of the parents to perform the test could be influenced by their assessment of the children’s cognitive abilities. This could lead to testing children with lower IQ more frequently than those without obvious or outstanding impairment. Some studies highlight the impact of brain malformations such as hydrocephalus<sup>17</sup> or corpus callosum dysgenesis<sup>5</sup> on cognitive performance. In our study we clearly show that total IQ, as well as almost all subtests tested by WISC-IV/WAIS-IV and KABC, were lower in patients with SBA than with SBO and the average population (mean 100). We note that the statistical analysis has limited reliability due to a small number of patients in the subgroups. This is a limitation of the current study which should be addressed in future research.

Hydrocephalus is often described to have a negative effect on cognitive performance.<sup>18</sup> In our cohort only 8% of patients with SBA did not have a hydrocephalus. We found that the presence of a hydrocephalus is associated

with low performance in verbal comprehension, perceptual reasoning, and total IQ score. However, the low number of individuals without hydrocephalus render a clear correlation difficult. Stenogyria, the appearance of multiple small compacted gyri separated by shallow sulci, has been suggested to arise as a result of a drained hydrocephalus.<sup>19</sup> Strikingly, we could show that the presence of stenogyria correlates significantly with the total IQ score and is associated with a negative outcome in all cognitive domains in WISC-IV/WAIS-IV (verbal comprehension, perceptual reasoning, working memory, processing speed). Given the severe effects of stenogyria, the relationship between shunt placement including the type of valve used will need to be established.

Both hypoplasia and partial agenesis of the corpus callosum are associated with cognitive impairment in our cohort, independent of the affected corpus callosum subregion. This is in line with the study by Bayram et al.<sup>20</sup> We further delineate that corpus callosum hypoplasia has an influence on total IQ score and verbal comprehension while a partial agenesis of the corpus callosum affects the working memory. While almost all patients with SBA exhibited partial corpus callosum dysgenesis in the rostrum (28%), splenium (54%), truncus (45%), and genu (23%), only 4% had a normal corpus callosum. It is remarkable that in our cohort, in contrast to the study by Elgamal et al.,<sup>21</sup> none of the patients showed a total agenesis of the corpus callosum. It could be assumed that better imaging quality or additional assessment of diffusion tensor images leads to a different interpretation of corpus callosum abnormalities in individual cases.

The influence of an abnormal corpus callosum on cognitive function is still unclear. Similar to our results, Fletcher et al. found a correlation between the size of the corpus callosum and non-verbal abilities.<sup>22</sup> In contrast, Hommet et al. could not verify this relationship, and there was also no influence of ventricular dilation on cognitive function.<sup>23</sup> These dissimilar results could be explained by the larger cohort in our study group.

Little is known about cognitive function in the presence of midbrain malformations. A rare pontine tegmental cap dysplasia is associated with cognitive deficit.<sup>24</sup> After midbrain hematoma an impairment in cognition is observed. Here we demonstrate that midbrain (e.g. pons and/or mesencephalon) hypoplasia may have a significant influence on cognition impairment, especially on verbal competence. Although our cohort was significantly larger compared to previous studies, the number of cases did not allow us to

consider more complex statistical dependencies such as interactions of combined brain malformations with cognitive functions.

Previous studies have seen socio-economic status as an important predictor for cognitive outcome in children with spina bifida.<sup>25</sup> Because of the lack of social and economic data their possible influence on cognitive performance could not be considered in our study.

In conclusion, brain malformations occur predominantly in patients with SBA, and here stenogyria, pons, and mesencephalon hypoplasia are specifically associated with a poor cognitive outcome. This information could be helpful in discussing the prognosis of the disease with the parents of children with spina bifida. We suggest that the complexity and interaction of the multitude of brain malformations is more relevant than a single anomaly. Further prospective studies to address the cognitive profile in detail are warranted to help enrol specific support during education and therapy.

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## Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## SUPPORTING INFORMATION

The following additional material may be found online:

**Table S1:** Demographic characterization of the cohort

**Table S2:** Distribution of various spinal dysraphisms in patients with spina bifida

**Table S3:** Correlation of anatomical lesion levels with spinal abnormalities and cerebellar herniation with brain malformations

**Table S4:** Cranial MRI-based measurements of the clivus-base, tentorium-base, and tentorium-knick angles

**Table S5:** Lesion level and cognitive profile in patients with spina bifida

**Figure S1:** Study enrolment.

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# EACD Europe 2021

## Call for Abstracts is now open!

*Key dates:*

- 1 December 2020: Opening Call for Abstracts
- 31 January 2021: Abstract Submission deadline
- 15 March 2021: Notification to submitting authors
- 1 April 2021: Registration deadline presenting authors

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### Theme: Childhood Disability in a Changing World

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- 20 May 2021: Childhood Disability in the Era of COVID-19
- 27 May 2021: Care, Research and Innovation, the New Landscape of User-Professional Partnership
- 3 June 2021: Global Partnerships: Opportunities and Challenges
- 10 June 2021: The Future of Childhood Disability



## MALFORMACIONES CEREBRALES Y RENDIMIENTO COGNITIVO EN ESPINA BÍFIDA

### OBJETIVO

Caracterizar sistemáticamente las características radiológicas de los pacientes con espina bífida, su relación con la función cognitiva y las diferencias entre la espina bífida abierta (SBA) y la espina bífida oculta (SBO).

### MÉTODO

En un estudio retrospectivo de 265 pacientes (117 mujeres, 148 varones; mediana de edad en el momento de la obtención de imágenes 11 años, rango 1-47 años; SBA  $n = 206$ , SBO  $n = 59$ ), el fenotipo radiológico se evaluó mediante resonancia magnética (IRM) (SBA  $n = 171$ , SBO  $n = 59$ ). En 126 pacientes (SBA  $n = 116$ , SBO  $n = 10$ ) Kaufman Assessment Battery for Children (KABC) o Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV) y Wechsler Adult Intelligence Scale, Cuarta edición (WAIS-IV) fueron realizados.

### RESULTADOS

Los pacientes con espina bífida mostraron muchas malformaciones cerebrales, siempre presentes en la SBA pero rara vez en la SBO. Las malformaciones cerebrales más frecuentes en la SBA incluyen cuerpo caloso anormal (69%), protuberancia hipoplásica (50%) y mesencéfalo hipoplásico (20%). Los puntajes de CI cognitivo total estaban por debajo del promedio en 44% (KABC), en 49% (WISC-IV) de los niños con SBA, mientras que casi todos los niños con SBO obtuvieron al menos un puntaje promedio. La estenogiria ( $p = 0,006$ ), la hipoplasia de la protuberancia ( $p = 0,003$ ) y la hipoplasia del mesencéfalo ( $p = 0,01$ ) se correlacionan con una menor puntuación total de CI, incluida la comprensión verbal. Varias malformaciones cerebrales se correlacionan significativamente con varios dominios cognitivos, pero el nivel de la lesión individual se correlaciona con la velocidad del proceso cognitivo.

### INTERPRETACIÓN

Las puntuaciones de CI fueron significativamente más bajas en pacientes con SBA que en pacientes con SBO. La competencia verbal, el razonamiento perceptivo y la memoria de trabajo serán dañados significativamente por la SBA y se correlacionarán con estenogiria y las anomalías del mesencéfalo y el cuerpo caloso.

## MALFORMAÇÕES CEREBRAIS E DESEMPENHO COGNITIVO EM ESPINHA BÍFIDA

### OBJETIVO

Caracterizar sistemáticamente os aspectos radiológicos de pacientes com espinha bífida, sua relação com a função cognitiva, e diferenças entre espinha bífida aberta (EBA) e espinha bífida oculta (EBO).

### MÉTODO

Em um estudo retrospectivo de 265 pacientes (117 do sexo feminino, 148 do sexo masculino; idade mediana no momento da imagem 11a, variação 1–47a; EBA  $n=206$ , EBO  $n=59$ ), o fenótipo radiológico foi avaliado por meio de exame de ressonância magnética (ERM) (EBA  $n=171$ , EBO  $n=59$ ). Em 126 pacientes (EBA  $n=116$ , EBO  $n=10$ ) a Bateria Kaufman de Avaliação para Crianças (BKAC) ou Escala Wechsler de Inteligência para Crianças, Quarta edição (WISC-IV) e Escala Wechsler de Inteligência para Adultos, Quarta edição (WAIS-IV) foram realizadas.

### RESULTADOS

Pacientes com espinha bífida mostram numerosas malformações cerebrais, sempre presentes em EBA, mas raramente em EBO. As malformações mais frequentes em EBA incluem corpo caloso anormal (69%), ponte hipoplásica (50%), e mesencéfalo hipoplásico (20%). Escores cognitivos totais estavam abaixo da média em 44% (BKAC) a 49% (WISC-IV) de crianças com EBA, enquanto a maioria das crianças com EBO pontuou pelo menos na média. Estenogiria ( $p=0,006$ ), hipoplasia da ponte ( $p=0,003$ ), e do mesencéfalo ( $p=0,01$ ) correlacionaram com menor escore total de QI e compreensão verbal. Várias malformações cerebrais correlacionam significativamente com vários domínios cognitivos, enquanto o nível da lesão apenas se correlaciona com a velocidade de processamento.

### INTERPRETAÇÃO

Escores de QI foram significativamente menores em pacientes com EBA do que em pacientes com EBO. A competência verbal, raciocínio perceptual, e memória de trabalho foram significativamente afetadas em EBA e correlacionadas com estenogiria e anormalidades no cérebro médio e corpo caloso.