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ORIGINAL ARTICLE

Effect of cervical and lumbosacral spina bifida cystica on volumes of intracranial structures in children

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Abstract

Purpose Spina bifida is a major disorder that occurs when the membranes of the spinal cord and medulla fail to close during the embryonic period and affects the individual for the rest of life. Some physical, mental, and social difficulties can be observed in the lives of children with spina bifida after surgery. The aim of this study is to determine what kind of volumetric changes occur in the brain when spina bifida occurs in different regions of the cord.

Methods The volume of intracranial structures of 14 children aged 1 to 9 years (7 cervical, 7 lumbosacral) with different levels of spina bifida compared with vol2Brain.

Results Spina bifida occurring in the cervical region was found to cause a greater volumetric reduction in subcortical structures, cortex and gyrus than spina bifida occurring in the lumbosacral region.

Conclusion We believe that our study will help clinicians involved in the management of this disorder.

Keywords Cervical · Intracranial volume · Lumbosacral · Spina bifida · vol2Brain

Introduction

Neural tube defects (NTDs) are medical conditions, including two common types—spina bifida and anencephaly—that result when the spinal cord and meninges fail during the third week of embryonic development [1]. Two typical types of spina bifida exist: spina bifida cystica (SBC) and spina bifida occulta [2]. SBC is associated with more severe symptoms. It includes meningocele and myelomeningocele. In meningocele, the spinal membranes form a sac. However, in myelomeningocele, the spinal membranes form a sac and the medulla spinalis enters into this sac. Therefore, myelomeningocele's clinical course is typically more severe. Although this condition is more common in the lumbar region, it can also occur in the upper parts of the vertebral canal. The prevalence of this condition varies from continent to continent and ranges from 1 to 3–5 per 1000 births from west to east, respectively [3]. SBC causes both physical and mental problems in children. Common physical problems include scoliosis, limb weakness and paralysis, bladder, bowel and skin problems, as well as eye movement abnormalities [4]. Common mental problems include low IQ scores, learning difficulties and reduced academic skills [5]. The negative effects of SBC on the central nervous system are partly known. In children with SBC, decreases in the amount of corpus callosum can be observed [6]. In addition, defects in gray matter tracts, shrinkage of the cerebellum and hydrocephalus have been reported in previous studies [7].

Hasan et al. found abnormalities in the main white matter tracts in children with hydrocephalus associated with myelomeningocele by using diffusion tensor imaging (DTI) data [8]. Treble et al. found thickness differences in different regions of the cerebral cortex in patients with myelomeningocele and demonstrated the negative effects of

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myelomeningocele on IQ [9]. These researchers also associated reduced hippocampus and amygdala volume with impaired prospective and episodic memory in patients with myelomeningocele [10].

Gray and white matter changes in patients with meningocele and myelomeningocele spina bifida were compared with healthy controls. The extent to which the level of spina bifida causes volumetric changes in intracranial structures has not yet been adequately explained. We hypothesise that lumbosacral and cervical SBC have different effects on the volume of intracranial structures. To test our hypothesis, we investigated the differences in intracranial volume in children diagnosed with lumbosacral spina bifida cystica (LS-SBC) and cervical spina bifida cystica (C-SBC).

Material and method

Inclusion criteria

The study started after the meeting of Erciyes University Clinical Research Ethics Committee on April 20, 2022, with the decision number 2022/338. Retrospective MRI data of 2000 patients diagnosed with NTD between the years 2000 and 2022 at Erciyes University Medical Faculty Pediatric Hospital were scanned. MRI data of 1986 children diagnosed with craniorachischisis, exencephaly-anencephaly, encephalocele, hydrocephalus, Chiari malformations type I–II, and other central nervous system disorders were excluded. MR images of children aged 1–9 years ($n=14$) with lumbosacral ($n=7$) and cervical ($n=7$) SBC were compared with vol2Brain. Of the 7 children with LS-SBC, 4 were girls and 3 were boys. Similarly, of the 7 children with C-SBC, 4 were boys and 3 were girls. The mean ages of both groups were 5.8 and 5 years old, respectively.

MR protocol

Neuroimaging was performed using a 1.5-T Siemens Aera scanner (Siemens, Germany). Anatomical images were acquired in the sagittal plane using a T1-weighted 3D Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequence with the following parameters: TR/TE = 1900/2.84 ms, flip angle = 5°, acquisition matrix = 256 × 256, FOV = 280 × 280 mm^2, number of slices = 160 and slice thickness = 1.0 mm.

MR data's analysis

According to the previously mentioned protocol, the T1-MPRAGE 3D volume files of children diagnosed with SBC were obtained with permission from Erciyes University Children's Hospital, Department of Radiology. MRI data were then converted into zip file in NII format by using dcm2nii https://www.nitrc.org/projects/dcm2nii/) and Radiant software (https://www.radiantviewer.com/). The resulting zip file was uploaded to the vol2Brain website (https://www.volbrain.net). vol2Brain analysis is based on an advanced pipeline that enables automatic segmentation of different brain structures from T1-weighted MRI (Fig. 1). Once the segmentation is performed, the final report is received (Fig. 2).

Statistical analysis

The data in the final report obtained with vol2Brain were processed into IBM SPSS Statistics 22 software. Non-parametric data were shown as median (minimum–maximum). Independent variables were evaluated with the Mann–Whitney U test ($^*p<0.05$, $^{**}p<0.001$). Graphs were created with the GraphPad Prism.

Results

Statistical comparisons of intracranial structures between patients with LS-SBC and C-SBC are shown in Table 1. Total (T), right (R), and left (L) nucleus accumbens volumes showed a statistically significant difference when compared between LS-SBC and C-SBC groups ($p<0.05$). While there were significant differences between groups in T amygdala and R amygdala volumes ($p<0.05$), no significant difference was found in L amygdala ($p>0.05$). There was a statistically significant difference in L and R fusiform gyrus volumes ($p<0.05$), and there was also a highly significant ($p<0.01$) statistical difference between groups in R fusiform gyrus volumes. While there was no statistically significant difference in R planum tempolare volume, T and L planum tempolare volumes were significantly lower in children with C-SBC than in children with LS-SBC ($p<0.05$). A similar statistical difference in planum tempolare volume was also found for the temporalis transversus gyrus (T and L; $p<0.05$, R; $p>0.05$).

Superior parietal lobule volume showed a statistically significant difference between groups in the T and R hemispheres ($p<0.05$). The volume of the L superior parietal lobule had a high significant difference ($p<0.01$). While the volume of the fusiform gyrus had a statistically significant difference between the groups in the T and R hemispheres ($p<0.05$), there was no significant difference in the L hemisphere ($p>0.05$). Limbic cortex had a statistically significant difference only in the L hemisphere ($p<0.05$), and there was no statistically significant difference in the T and R hemispheres. The entorhinal area showed a statistically significant difference between the groups in the volumes of the T, R, and L hemispheres ($p<0.05$). The medial part of the cingular gyrus showed a statistically significant

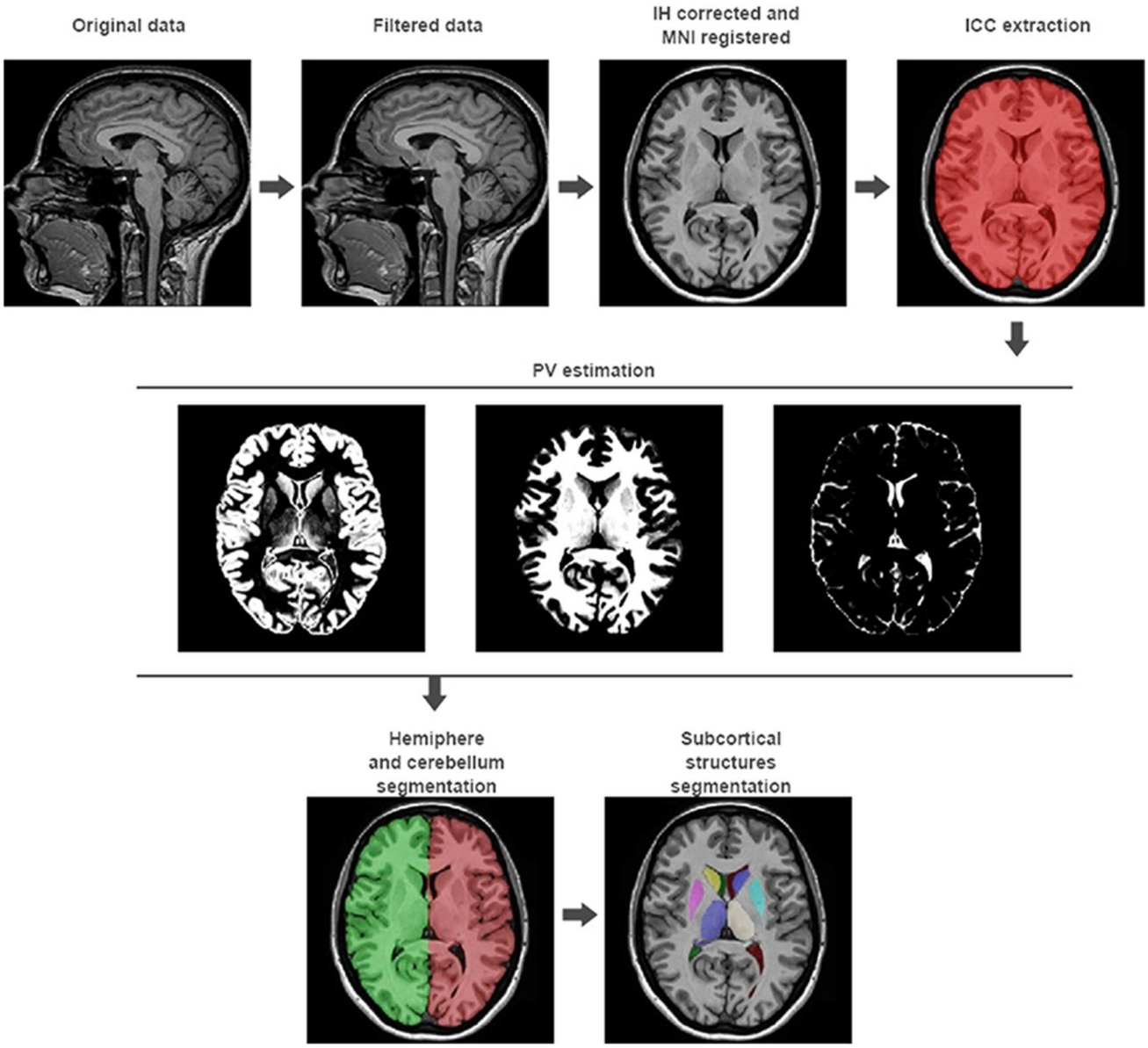

Fig. 1 Processing pipeline for vol2Brain [11]. The pre-processing of the MR images is carried out in a 5-step process. Denoising step with an adaptive non-local mean filter, an affine registration in the Montreal Neurological Institute (MNI) space, a correction of the image inhomogeneities, and an intensity normalisation. Afterwards, MRI images are segmented in the MNI space using non-local patch-based multi-atlas method [12]

difference between the groups in the T and L hemispheres ($p < 0.05$). This significant difference was not found in other cingular regions.

There was a statistically significant difference between groups in the volume of the T and L gyrus parahippocampalis ($p < 0.05$) and a highly significant difference in the R hemisphere ($p < 0.01$). When the insula was examined, there was a statistically significant difference in volume between the groups in both the anterior insula and the L hemisphere of the posterior insula ($p < 0.05$). No significant difference was found in other insular regions. Finally, there was a statistically significant difference between the groups in the lateral ventricle of the R hemisphere ($p < 0.05$). No statistically significant differences were found between the groups in the other ventricles.

Discussion

Dennis et al. found that spina bifida occurring above the thoracic level reduced white and gray matter volume in the cerebellum compared to lower levels [13]. In our study, no significant difference was found in the total volume of

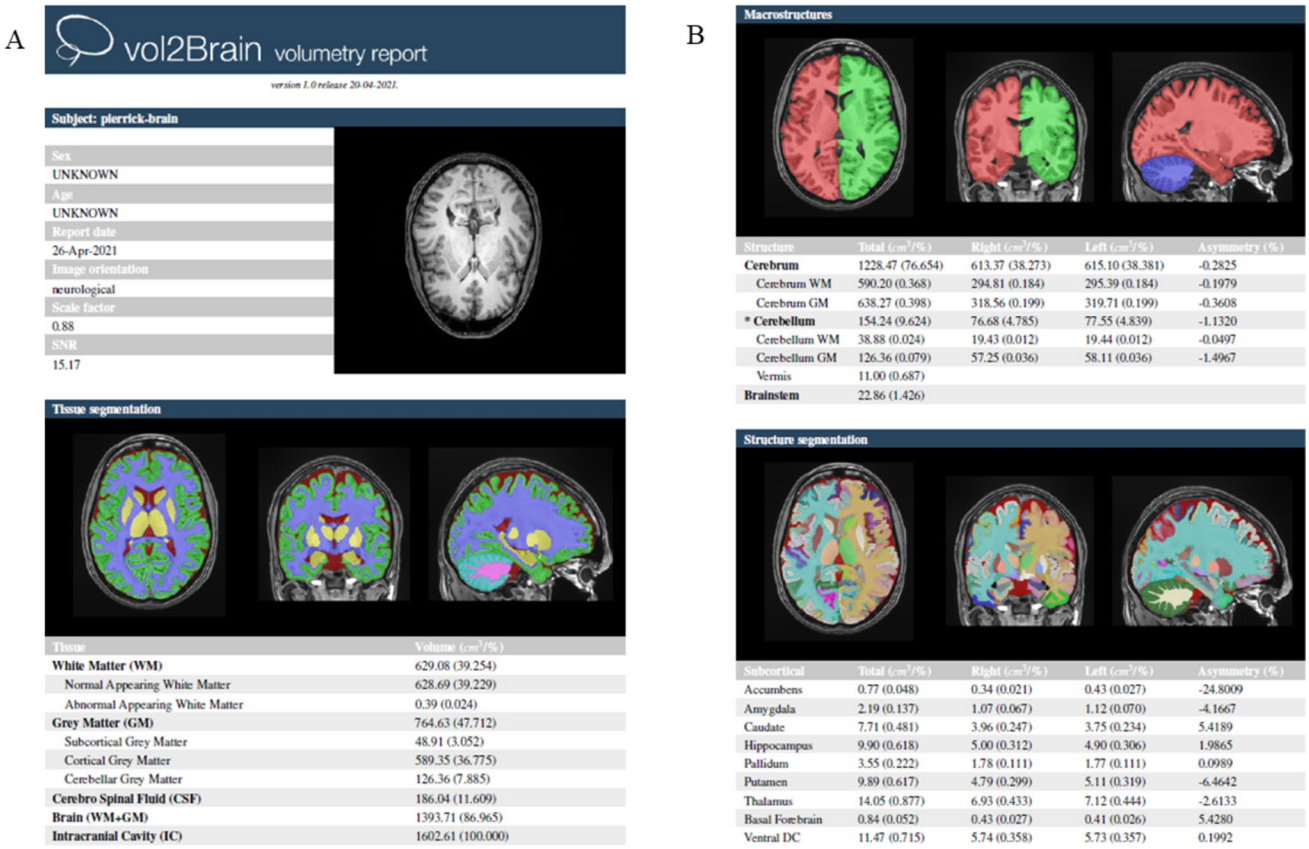

Fig. 2 An example of a vol2Brain pdf report. The report consists of several sections. **A** At the top is the hidden patient data, including age and gender with a randomly assigned number. Macrostructures such as WM, GM, CSF, adn IC are listed after a patient data. **B** Structures such as putamen, caudate, pallidum, thalamus, hippocampus, amygdala, and nucleus accumbens are listed on the next page. Values are expressed in cubic centimeters and percentages. A visual example of axial, sagittal, and coronal views is provided in the pdf report to document quality [11]

the cerebellum (Fig. 3a). Children with C-SBC had more white matter (Fig. 3c) and less gray matter in the cerebellum compared to children with LS-SBC (Fig. 3b). Fletcher et al. showed that volume reduction in the cerebral structures as well as in the cerebellum was exacerbated by upper level lesions [14]. In our study, there were decreases in total gray matter (Fig. 4a), cortical gray matter (Fig. 4b), and subcortical gray matter (Fig. 4c) volumes in the cerebrum, but these were not statistically significant. It was interesting to note that the reduction in gray matter was accompanied by an increase in white matter volume (Fig. 5a). Although the proportion of abnormal white matter in children with C-SBC was higher than in those with LS-SBC, the difference was not statistically significant (Fig. 5b). According to Fletcher et al., one of the reasons for the volume reduction in cerebral and cerebellar structures is the penetration of amniotic fluid into the spinal lesion of the fetus and the pressure of this fluid on the neurological structures [15]. In our study, the level of lesion did not cause any change in total brain volume, but there was a decrease in gray matter and an increase in white matter as the lesion level increased. Spina bifida patients with hydrocephalus usually have abnormal increases in the amount of cerebrospinal fluid (CSF). In our study, total CSF (Fig. 6a), lateral ventricle (Fig. 6b), inferior lateral ventricle (Fig. 6c), 3rd ventricle (Fig. 6d), and 4th ventricle volumes (Fig. 6e) were surprisingly increased in children with C-SBC compared to children with LS-SBC. Although these volumetric differences were not statistically significant, they clearly indicate that the lesion in the upper regions directly increases CSF and ventricular volumes.

The nucleus accumbens is known to play a role in events such as motivation, disgust and reinforcement learning [16]. In an fMRI study in rats, it was found that the nucleus accumbens of mother rats living with their offspring was highly active [17], while another study found that lesions in this region negatively affected maternal behavior [18]. In our study, the nucleus accumbens volume was 40% lower in children with C-SBC compared to children with LS-SBC (Fig. 7a). The amygdala is a structure responsible for memory, decision making and emotional behavior. It is known

Table 1 Statistical data on volumetric differences in intracranial structures in patients with cervical and lumbosacral SBC

Brain region	Lumbosacral SBC ($n=7$) Median (mm^3) (min–max)	Cervical SBC ($n=7$) Median (mm^3) (min–max)	Sig. (p)
Accumbens T*	0.070 (0.06–0.20)	0.05 (0.01–0.20)	0.035
Accumbens R*	0.03 (0.03–0.10)	0.02 (0.01–0.11)	0.035
Accumbens L*	0.03 (0.03–0.10)	0.02 (0.01–0.10)	0.035
Amygdala T*	0.14 (0.13–0.23)	0.06 (0.03–0.15)	0.018
Amygdala R*	0.07 (0.05–0.12)	0.03 (0.01–0.07)	0.018
Fusiform gyrus T*	2.11 (1.34–2.45)	1.12 (0.35–1.69)	0.013
Fusiform gyrus R**	1.03 (0.66–1.13)	0.57 (0.10–0.90)	0.009
Fusiform gyrus L*	1.05 (0.68–1.42)	0.54 (0.25–0.81)	0.025
Planum tempolare T*	0.37 (0.26–0.38)	0.27 (0.14–0.35)	0.035
Planum tempolare L*	0.19 (0.12–0.21)	0.14 (0.10–0.20)	0.035
Transverse temporal gyrus T*	0.19 (0.17–0.29)	0.16 (0.05–0.22)	0.035
Transverse temporal gyrus R*	0.12 (0.10–0.16)	0.08 (0.02–0.15)	0.035
Sup. parietal lobule T*	2.17 (1.92–2.91)	1.93 (1.30–2.17)	0.018
Sup. parietal lobule R*	1.06 (0.88–1.35)	0.96 (0.56–1.06)	0.035
Sup. parietal lobule L**	1.12 (1.02–1.56)	0.97 (0.65–1.11)	0.004
Occipital fusiform gyrus T*	0.59 (0.44–0.72)	0.40 (0.23–0.65)	0.025
Occipital fusiform gyrus R*	0.36 (0.22–0.62)	0.21 (0.10–0.33)	0.013
Limbic cortex L*	2.44 (1.84–3.00)	1.69 (0.88–2.98)	0.035
Entorhinal area T*	0.43 (0.29–0.57)	0.28 (0.16–0.44)	0.013
Entorhinal area R*	0.22 (0.14–0.32)	0.13 (0.07–0.24)	0.013
Entorhinal area L*	0.20 (0.16–0.25)	0.13 (0.07–0.24)	0.018
Middle cingulate gyrus T*	1.10 (0.93–1.35)	0.76 (0.19–1.26)	0.035
Middle cingulate gyrus L*	0.62 (0.45–0.79)	0.38 (0.09–0.67)	0.035
Parahippocampal gyrus T*	0.59 (0.41–0.74)	0.39 (0.10–0.58)	0.013
Parahippocampal gyrus R**	0.29 (0.19–0.42)	0.17 (0.03–0.26)	0.009
Parahippocampal gyrus L*	0.32 (0.22–0.34)	0.21 (0.07–0.33)	0.025
Anterior insula L*	0.41 (0.31–0.49)	0.25 (0.09–0.47)	0.025
Posterior insula L*	0.17 (0.14–0.26)	0.13 (0.07–0.19)	0.025
Lateral Ventricle R**	0.01 (0.00–0.08)	0.10 (0.02–0.54)	0.009

Non-parametric data were shown as median (minimum–maximum). Independent variables were evaluated with the Mann–Whitney U test (*$p<0.05$, **$p<0.001$)

SBC spina bifida cystica, *Sup* superior, *T* total, *R* right, *L* left

that there is a significant decrease in amygdala volume especially in patients with major depression [19]. In our study, children with C-SBC had 60% less amygdala volume than children with LS-SBC (Fig. 7b).

The fusiform gyrus is a structure involved in the recognition of facial and body contours, word recognition and color processing [20, 21]. In our study, the volume of the fusiform gyrus was approximately 50% smaller in children with C-SBC compared to children with LS-SBC. A volumetric difference of 30% was found in the occipital part of the fusiform gyrus (Fig. 7c).

The planum tempolare (PT) is a triangular area that forms the heart of Wernicke's area, one of the most important functional areas for language. This region, which is associated with word processing, has been reported to be larger in children and adolescents with autism. On the other hand, another study found that the left planum temporale has a lower volume in autism [22]. In our study, the median T and L PT volumes were 30% lower in children with C-SBC compared to children with LS-SBC (Fig. 7d).

The transverse temporal gyrus (TTG) is known as the primary auditory cortex (Brodmann areas 41–42 = Heschl's gyrus). This area has been shown to be active in tonal and semantic processes in fMRI [23]. A neuroimaging study found a volumetric reduction in the TTG in patients with tinnitus [24]. In our study, TTG volume was 30% lower in children with C-SBC than in children with LS-SBC (Fig. 7e).

The superior parietal lobule is an important region located just posterior to the gyrus postcentralis and receives fibres from the cingulum, medial, and superior longitudinal fasciculi, especially the occipital lobe. Lesions in this region may result in astereognosis and hemispatial defects. Wilson's

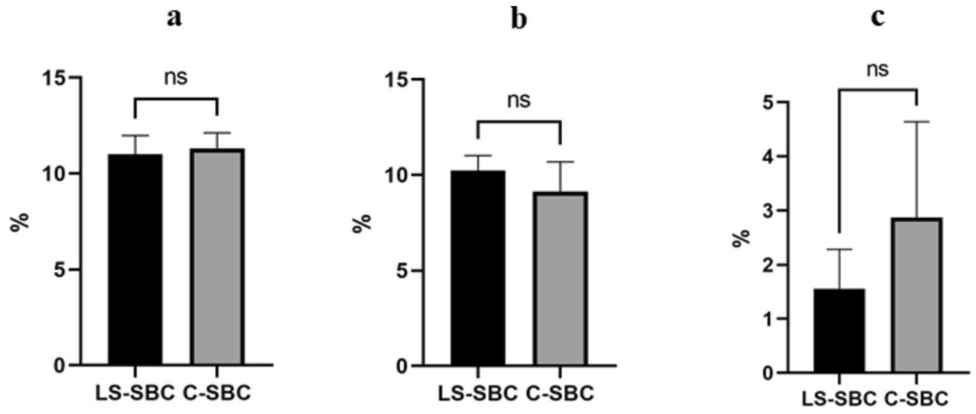

Fig. 3 Total volume, white matter, and gray matter ratios of the cerebellum. **a** Ratio of total cerebellum volume to total intracranial volume. **b** Ratio of gray matter volume in the cerebellum to total intracranial volume. **c** Ratio of white matter volume in the cerebellum to total intracranial volume. LS-SBC lumbosacral spina bifida cystica, C-SBC cervical spina bifida cystica. Non-parametric data were shown as median (minimum–maximum). Independent variables were evaluated with the Mann–Whitney *U* test (*$p<0.05$, **$p<0.001$, ns: statistical insignificance)

disease is characterised by cardiovascular disorders, learning difficulties and developmental delay. A decrease in superior parietal lobe volume has been reported in these patients [25]. In our study, 10% less volume was observed in children with C-SBC compared to children with LS-SBC (Fig. 7f).

The limbic cortex consists of gray matter masses forming the shell of the limbic system, including the entorhinal area, cingulum and parahippocampal gyrus. Studies of schizophrenia are based on the view that there is an abnormality in limbic structures. Many review studies have found an abnormality in the entorhinal cortex of post-mortem schizophrenia patients and a reduction in the volume of entorhinal and hippocampal regions [26]. Lepage et al. found that National Football League (NFL) players who were frequently exposed to head trauma had decreased volume in the amygdala, hippocampus and cingulate gyrus and suggested that this volume reduction may be an important biomarker for chronic traumatic encephalopathy [27]. Our study revealed that children with C-SBC have a significant decrease in the volume of their limbic system when compared to children with LS-SBC. Specifically, we observed a 30% reduction in the volume of the limbic cortex (Fig. 7g), a 40% reduction in the entorhinal area (Fig. 7h), a 40% reduction in the medial cingulate cortex (Fig. 7i), and an approximately 30% reduction in the parahippocampal region (Fig. 7j).

The insula is a part of the brain responsible for regulating emotional responses and promoting self-awareness.

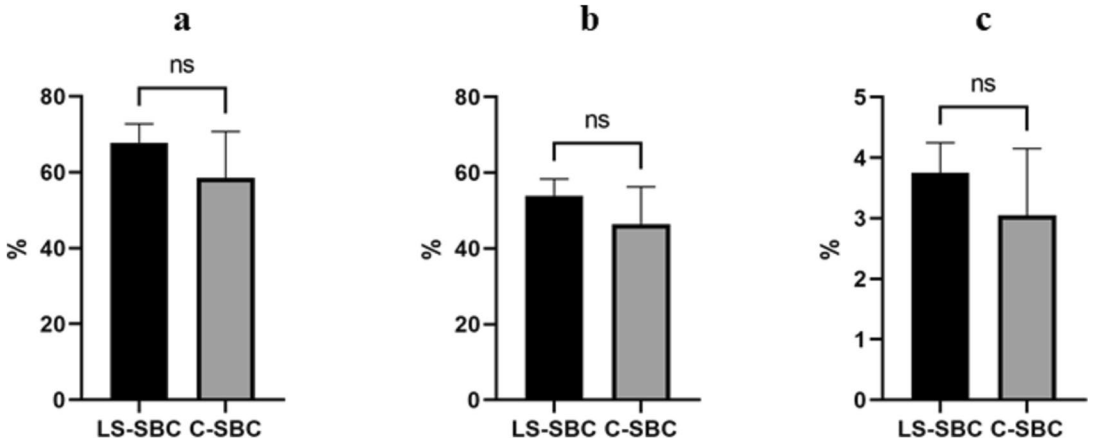

Fig. 4 Ratio of total gray matter, cortical gray matter, and subcortical gray matter to total intracranial volume. **a** Ratio of total gray matter to total intracranial volume. **b** Ratio of cortical gray matter to total intracranial volume. **c** Ratio of subcortical gray matter to total intracranial volume. LS-SBC lumbosacral spina bifida cystica, C-SBC cervical spina bifida cystica. Non-parametric data were shown as median (minimum–maximum). Independent variables were evaluated with the Mann–Whitney *U* test (*$p<0.05$, **$p<0.001$, ns: statistical insignificance)

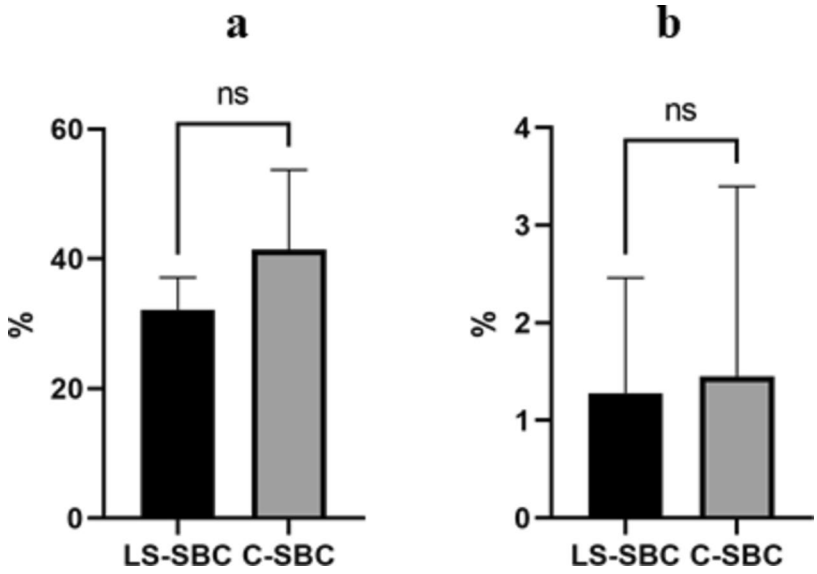

Fig. 5 Ratio of total white matter and abnormal white matter to total intracranial volume. **a** Ratio of total white matter to total intracranial volume. **b** Ratio of abnormal white matter to total intracranial volume. LS-SBC lumbosacral spina bifida cystica, C-SBC cervical spina bifida cystica. Non-parametric data were shown as median (minimum–maximum). Independent variables were evaluated with the Mann–Whitney *U* test (*$p < 0.05$, **$p < 0.001$, ns: statistical insignificance)

According to a study conducted by Guiliani et al., suppressing emotional expression was found to be positively linked to an increase in the volume of the anterior insular region [28]. In our research, we discovered that children diagnosed with C-SBC had a 40% lower volume of the anterior left insula in comparison to children with LS-SBC. Moreover, our study revealed a 25% reduction in the volume of the posterior insula in children with C-SBC (Fig. 7k).

The biggest challenge in our study was the lack of detailed volumetric analysis studies in children with spina bifida at an early age. Most of the available studies focused on the total brain volume or large structures such as the midbrain, pons, and cerebellum. This made it difficult for us to compare small brain regions with other studies. Additionally, the sample size in our study was very small. This was mainly due to the fact that spina bifida is usually associated

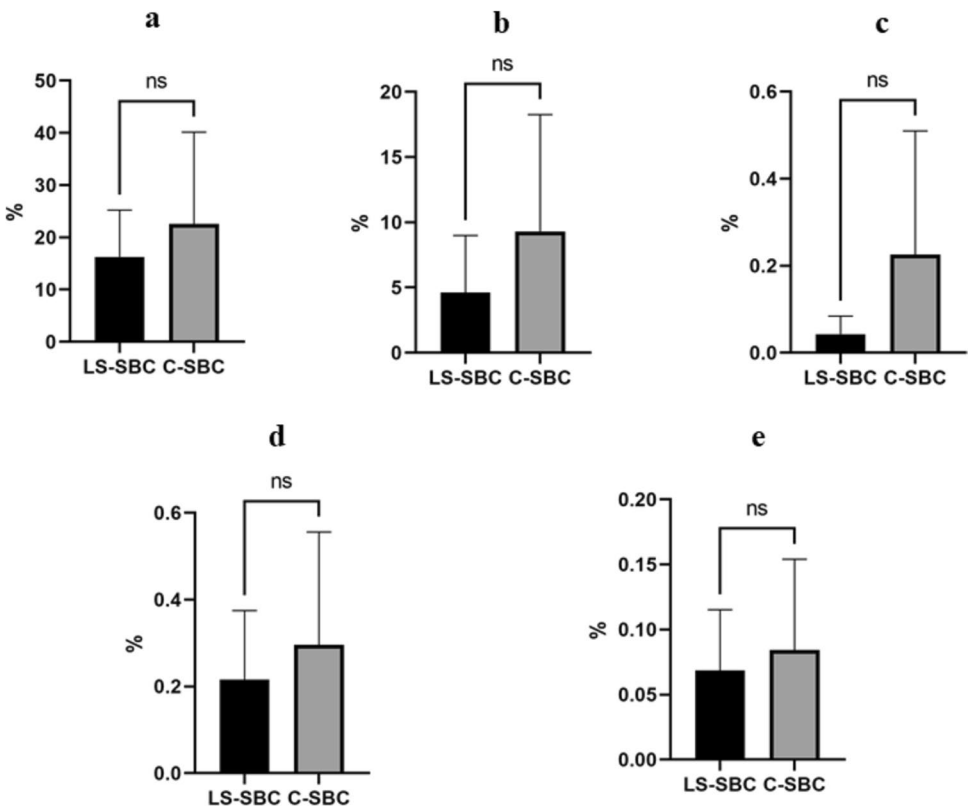

Fig. 6 Ratio of cerebrospinal fluid and ventricular volumes to total intracranial volume. **a** Ratio of total cerebrospinal fluid to total intracranial volume. **b** Ratio of lateral ventricles to total intracranial volume. **c** Ratio of inferior lateral ventricles to total intracranial volume. **d** Ratio of 3rd ventricle volume to total intracranial volume. **e** Ratio of 4th ventricle volume to total intracranial volume. LS-SBC lumbosacral spina bifida cystica, C-SBC cervical spina bifida cystica. Non-parametric data were shown as median (minimum–maximum). Independent variables were evaluated with the Mann–Whitney *U* test (*$p < 0.05$, **$p < 0.001$, ns: statistical insignificance)

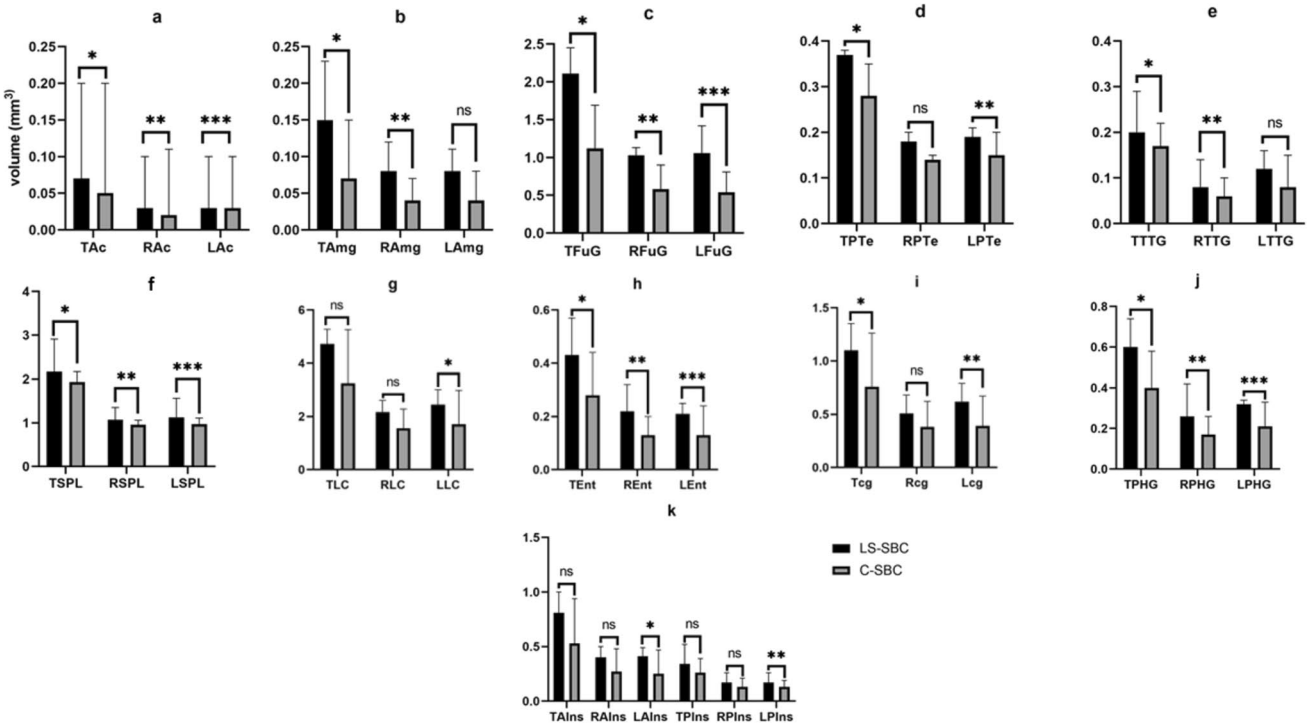

Fig. 7 Volumetric differences in intracranial structures of patients with lumbosacral and cervical SBC. **a** Nuc. accumbens. **b** Amygdala. **c** Fusiform gyrus. **d** Planum temporale. **e** Transverse temporal gyrus. **f** Superior parietale lobule. **g** Limbic cortex. **h** Entorhinal area. **i** Anterior cingular cortex. **j** Parahippocampal gyrus. **k** Anterior and posterior insula. Non-parametric data were shown as median (minimum–maximum). Independent variables were evaluated with the Mann–Whitney *U* test. *, **, *** mean the variable showing significance; $p < 0.05$. TAc total nuc. accumbens, RAc right nuc. accumbens, LAc left nuc. accumbens, TAmg total amygdala, RAmg right amygdala, LAmg left amygdala, TFuG total fusiform gyrus, RFuG right fusiform gyrus, LFuG left fusiform gyrus, TPTe total planum temporale, RPTe right planum temporale, LPTe left planum temporale, TTTG total transverse temporal gyrus, RTTG right transverse temporal gyrus, LTTG left transverse temporal gyrus, TSPL total superior parietal lobule, RSPL right superior parietal lobule, LSPL left superior parietale lobule, TLC total limbic cortex, RLC right limbic cortex, LLC left limbic cortex, TEnt total entorhinal area, REnt right entorhinal area, LEnt left entorhinal area, Tcg total middle cingulate gyrus, Rcg right middle cingulate gyrus, Lcg left middle cingulate gyrus, TPHG total parahippocampal gyrus, RPHG right parahippocampal gyrus, LPHG left parahippocampal gyrus, TAIns total anterior ınsula, RAIns right anterior ınsula, LAIns left anterior ınsula, TPIns total posterior ınsula, RPIns right posterior ınsula, LPIns left posterior ınsula, LS-SBC lumbosacral spina bifida cystica, C-SBC cervical spina bifida cystica

with different clinical presentations such as exencephaly, anencephaly, and hydrocephalus, which we did not include in our study. Furthermore, the patients in our study did not have DTI data, which would have allowed us to show how the pathways in the brain are affected in children with C-SBC and LS-SBC. As this was a pilot study, we believe that larger samples should be studied to generalise the results of the study.

Conclusions

In our study, as the region of the spine where the spina bifida occurred progressed upward, volume reductions in cerebral structures became more noticeable. The negative impact of spina bifida on volume of intracranial structures was greater at higher levels than at lower levels. In children, cervical spina bifida was found to cause an increase in ventricular volume, an increase in CSF, and volumetric decreases in some basal nuclei, gray matter and gyrus compared to lumbar spina bifida. In contrast to previous studies, there was no change in total brain volume. However, the main reason for the unchanged total brain volume was, surprisingly, the decrease in the proportion of gray matter, which was compensated by an increase in the proportion of white matter. Children with spina bifida have a hard time adjusting to their families, their schools, and their social lives. We believe that all clinicians involved in the rehabilitation process of these children, from surgical operations to psychological support, should consider the level of spina bifida lesion, which will contribute to the recovery process of these children.

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Author contributions Hüseyin Yiğit wrote the manuscript, created the graphics, and reviewed the literature. Hatice Güler contributed to the manuscript writing and literature review, created the project. Halil Yılmaz made the statistical analysis and contributed to the manuscript writing and literature review. Ümmügülsüm Özgül Gümüş, Zehra Filiz Karaman, and Tamer Güneş assisted in patient selection and ensured the acquisition of radiological images and contributed literature review.

Data availability Data is available upon reasonable request.

Declarations

Conflict interest The authors have no relevant financial or non-financial interests to disclose.

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