RESEARCH ARTICLE OPEN ACCESS

Macrostructural Brain Abnormalities in Spinal Muscular Atrophy

A Case-Control Study

Emilie Groulx-Boivin, MD, Andrea Oliveira-Carneiro, MSc, Helen Carlson, PhD, Amalia Floer, Adam Kirton, MD, MSc, Jean Mah, MD, MSc, Christine Saint-Martin, MD, MSc, Roberta La Piana, MD, PhD, and Maryam Oskoui, MD, MSc

Correspondence
Dr. Groulx-Boivin
emilie.groulx-boivin@mail.mcgill.ca

Neurol Genet 2024;10:e200193. doi:10.1212/NXG.0000000000200193

Abstract

Background and Objectives

Most individuals with spinal muscular atrophy (SMA) on disease-modifying therapies continue to have chronic motor impairment. Insights into brain involvement in SMA may open new pathways for adjunctive therapies to optimize outcomes. We aimed to characterize macrostructural brain abnormalities detected by MRI in individuals with SMA compared with peer controls.

Methods

We conducted a cross-sectional case-control study of children and adults with a confirmed genetic diagnosis of 5q SMA, and peer controls matched by age and sex. Brain MRIs acquired on a 3T MRI scanner through a standardized research protocol were reviewed to qualitatively assess the presence of macrostructural changes. The primary outcome was the presence of any structural brain anomaly on MRI. In addition, the total volume of each participant's lateral ventricles was quantified by volumetry using MRIcron. Genetic and clinical variables, including *SMN2* copy number and motor function (Hammersmith Functional Motor Scale Expanded and Revised Upper Limb Module scores), were then correlated with neuroimaging findings.

Results

A total of 42 participants completed the study (mean age 17.4, range 7–40; 67% male). Of the 21 individuals with 5q SMA, 9 (43%) had macrostructural brain abnormalities identified on MRI compared with 2 of 21 (10%) peer controls (odds ratio 7.1, 95% confidence interval 1.4–34.0). In patients with SMA, the most common structural changes were widening of the arachnoid spaces (n = 4) and ventriculomegaly (n = 4). Individuals with SMA had larger median lateral ventricular volume than their normally developing peers (9.3 mL, interquartile range [IQR] 5.5–13.1 vs 5.3 mL, IQR 3.8–9.8; $p = 0.034$). Structural brain abnormalities were more frequent in those with 2 *SMN2* copies (3/5, 60%) compared with 3 or 4 *SMN2* copies (4/10, 40% and 2/6, 33% respectively), not reaching significance. We found no association between structural changes and motor function scores.

Discussion

Individuals with SMA have higher rates of macrostructural brain abnormalities than their neurotypical peers, suggesting CNS involvement in SMA. Understanding changes in the brain architecture of the SMA population can inform the development of adjunct therapies targeting the CNS and potentially guide rehabilitation strategies.

From the Departments of Pediatrics and Neurology and Neurosurgery (E.G.-B., M.O.), Montreal Children's Hospital, McGill University; Research Institute (A.O.-C., M.O.), McGill University Health Centre, Montreal, Quebec; Alberta Children's Hospital Research Institute (H.C., A.F., A.K., J.M.); Department of Pediatrics (H.C., A.F., A.K., J.M.), Cumming School of Medicine, University of Calgary, Alberta; Division of Pediatric Medical Imaging (C.S.-M.), Department of Radiology, Montreal Children's Hospital; Department of Neurology and Neurosurgery (R.L.P.), Montreal Neurological Institute; and Department of Diagnostic Radiology (R.L.P.), McGill University, Montreal, Quebec, Canada.

Go to Neurology.org/NG for full disclosures. Funding information is provided at the end of the article.

The Article Processing Charge was funded by the authors.

Glossary

HFMSE = Hammersmith Functional Motor Scale Expanded; **IQR** = interquartile range; **RULM** = Revised Upper Limb Module; **SMA** = spinal muscular atrophy; **SMN** = survival motor neuron.

Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive disorder characterized by degeneration of lower motor neurons, leading to progressive muscle atrophy and weakness. SMA demonstrates significant clinical diversity, with 4 main phenotypes distinguished based on the age of symptom onset and attainment of developmental milestones. Estimated to affect 1 in 10,000 live births, SMA is most commonly caused by a homozygous deletion of the survival motor neuron 1 (*SMN1*) gene on chromosome 5q.[1] *SMN2*, a paralogous gene, is an important determinant of disease severity where a lower number of *SMN2* copies predict a more severe and earlier-onset phenotype.[1] In recent years, patients with SMA have gained access to several disease-modifying therapies such as nusinersen, onasemnogene abeparvovec, and risdiplam. Although these treatments have been associated with substantial improvements in survival and motor milestone acquisition, chronic motor impairment remains for most individuals with SMA.[2,3]

The role of lower motor neurons in SMA pathogenesis is widely recognized. However, emerging evidence from both animal and human studies has led to growing recognition of brain involvement in the disease. Using immunocytochemistry and in situ hybridization, multiple groups have demonstrated that *SMN* gene expression is not limited to the anterior horn of the spinal cord but rather widespread throughout the CNS.[4-6] In addition, studies using mouse models of severe SMA have shown reduced SMN protein levels and cell proliferation in certain brain areas such as the hippocampus and primary motor cortex.[7,8] In humans, cerebral involvement in SMA remains understudied.[9] Select case reports and case series of individuals with type 0 or type I SMA described diffuse cortical and subcortical atrophy, dilation of the ventricles, as well as abnormalities of various brain regions including the corpus callosum and cerebellum.[10-13] A few larger case-control neuroimaging studies focused on volumetric assessments such as cortical thickness and gray/white matter volume, lacking a comprehensive description of all types of structural brain abnormalities in SMA.[14-16]

The effects of early motor unit dysfunction on brain development in SMA also remain largely unknown. Gaining insights into brain involvement in SMA may open new pathways for adjunctive therapies to optimize outcomes in symptomatic patients. In addition, understanding the developmental plasticity that occurs in the face of motor disability, both at the individual and group levels, may assist in the identification of neurophysiologic substrates to guide rehabilitation in SMA. Therefore, we aimed to characterize macrostructural brain anomalies detected by MRI in individuals with SMA. The primary outcome was the presence of any macrostructural brain abnormality on MRI, and we hypothesized that the rate of these abnormalities would be higher in patients with SMA compared with controls.

Methods

Study Population

We conducted a cross-sectional case-control study of children and adults with SMA and normally developing peers matched by age (year of birth) and sex. Given the exploratory nature of the study, a convenience sample of 40 participants was planned. Participants were recruited from the Greater Montreal Area and Calgary through the McGill University Health Center Research Institute and the Alberta Children's Hospital, respectively. For the SMA group, we included individuals between the ages of 5–45 years with a confirmed genetic diagnosis of 5q SMA, 2–4 copies of the *SMN2* gene, and any status of disease-modifying therapy received. Peer controls were considered normally developing if they had no history of developmental or neurologic conditions and had not received rehabilitation or special education services during childhood or adolescence.

Exclusion criteria for both groups were (1) any other neurodevelopmental, neurogenetic, or acquired CNS condition, (2) contraindications to MRI or inability to comply to study procedures without sedation, or (3) dependence on permanent ventilatory support.

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the Research Ethics Board in both participating centers, and informed consent was obtained from all participants and parents/guardians where applicable.

Data Collection

Demographic and clinical variables were obtained through a structured chart review. For patients who received multiple disease-modifying therapies, the first treatment received was recorded. A trained physiotherapist evaluated the motor function of patients with SMA using the Hammersmith Functional Motor Scale Expanded (HFMSE) and the Revised Upper Limb Module (RULM) prior to the MRI. However, if the participant had recently (within 3 months of the imaging study) undergone a complete physical assessment, the motor scores were extracted from that evaluation rather than conducting a new one.

Brain MRI Acquisition

All brain MRIs were acquired using one of 2 3T MRI systems and a standardized research protocol. Patients with SMA and peer controls from Montreal were scanned at the Montreal Children's Hospital using a common MRI machine (Acheiva X, Philips Health care, Best, The Netherlands, 32-channel head coil), while those from Calgary were scanned using a second MRI machine (MR750w, GE Healthcare, Chicago, IL, 32-channel head coil). T1-weighted parameters were as follows: for Montreal, TE/TR = 3.5/7.9 ms, flip angle = 8°, 170 sagittal slices with field of view of 256 mm × 204 mm, and an acquisition matrix of 256 × 203 with voxel acquisition size being 1.0 mm × 1.0 mm x 1.0 mm and for Calgary, TE/TR = 3.2/8.5 ms, flip angle = 11°, 166 axial slices, matrix = 256 × 256, and voxel size = 1.0 mm isotropic. Anatomical T2-weighted and T2-FLAIR sequences were additionally obtained for each participant.

Structural MRI Review and Lateral Ventricle Volumetry

A single neuroradiologist, blinded to the participants' diagnoses, reviewed all images according to standard clinical practice to identify visible structural changes. All macrostructural brain abnormalities reported in this study, including ventriculomegaly, were determined through the neuroradiologist's qualitative assessment. As a complement to qualitative assessments, brain volumetry was used by one author (EGB) to quantify ventricular volume in a blinded evaluation. The semiautomated 3D fill tool of the MRIcron software[17] was used to map and measure the volume of each participant's lateral ventricles based on T1 image intensity (Figure 1). The right and left lateral ventricles were segmented and computed separately. The segmentation thresholds used to segment the lateral ventricles from the brain were a difference from origin and difference at edge of 30 (arbitrary units) and a radius of the initial seed sphere of 15–30 mm depending on individual anatomy. Manual adjustments in ventricle segmentation were performed using the drawing tools as required. We compared the median total lateral ventricular volume of each group. Volumes are expressed in milliliters (mL).

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics, Version 28.0. For continuous variables, the Shapiro-Wilk test was first used to assess normality, and then, patient characteristics were compared between groups using the Mann-Whitney *U* tests. Categorical variables were compared between groups using the χ^2 and Fisher exact as appropriate, and the MOVER-R Wilson confidence interval for the odds ratio. The Spearman Rank Order was used to evaluate the correlation between ventricular volume and motor scores. All tests of significance were conducted at a predetermined level of significance of 0.05.

Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Results

Participant Characteristics

A total of 42 participants, 28 children and 14 adults, completed the study procedures (Figure 2). There were no differences in sex, age, or handedness between patients with SMA and their peer controls (Table 1). Type II SMA was most prevalent (9/21, 43%), followed by type III (8/21, 38%) and type I SMA (4/21, 19%). All patients with SMA received disease-modifying therapy (Table 2). Five individuals with SMA (24%) could ambulate independently when assessed, while 76% were nonambulant.

For patients with type I SMA, the median age of symptom onset was 0.2 years (interquartile range [IQR] 0.1–0.5) and the median age of treatment initiation was 3.1 years (IQR 0.5–7.8). All 4 patients with type I SMA were fed exclusively via gastrostomy tube and required nighttime ventilation. Among them, 1 (25%) could sit with support, while the remaining 3 (75%) were limited to head control in best motor function. Of the 9 individuals with type II SMA, 4 (44%) used nocturnal ventilation, with one of them displaying a macrostructural brain abnormality (xanthogranuloma). Among the 8 participants with type III SMA, 1 (13%) used nighttime ventilation and had a normal brain MRI.

Structural Brain MRI Findings

Of 21 individuals with 5q SMA, 9 (43%) had macrostructural brain abnormalities identified on MRI compared with

Figure 1 Ventricle Volumetry Mapping

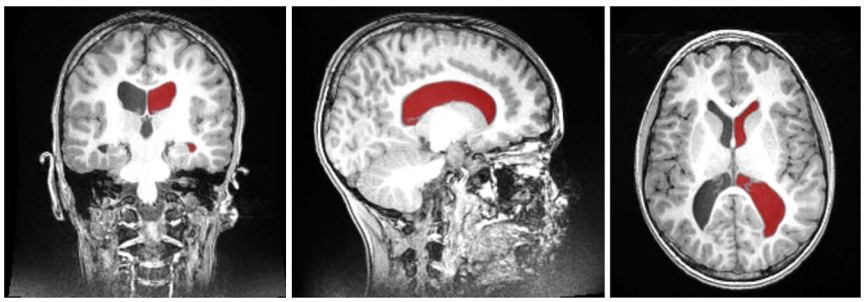
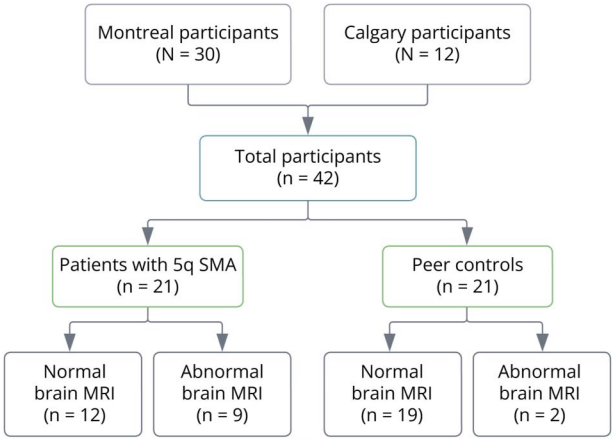


Illustration of volume mapping of the left lateral ventricle using MRIcron.

Figure 2 Participant Flowchart



Flow diagram of participants and MRI findings.

2 of 21 (10%) peer controls (odds ratio [OR] 7.1, 95% confidence interval [CI] 1.4–34.0). The observed structural changes are listed in Table 1, and examples are illustrated in Figure 3. The most commonly identified structural abnormalities were supratentorial ventriculomegaly and widening of the arachnoid spaces, each present in 4 of 9 (44%) SMA patients with abnormal brain MRI. One-third (3/9, 33%) of SMA patients with structural brain abnormalities had both supratentorial ventriculomegaly and widening of the arachnoid spaces. All 3 of these patients were diagnosed with type I SMA and had 2 *SMN2* copies. Using a more stringent definition of macrostructural abnormalities, excluding structural changes considered normal variants (e.g., arachnoid cyst and developmental venous anomaly), produced similar results: abnormalities were found in 8 of 21 (38%) patients with SMA and 1 of 21 (5%) controls ($p = 0.021$).

Table 2 summarizes the participant characteristics and motor function of the 21 patients with SMA, distinguished by normal vs abnormal brain MRI. As shown in Figure 4, among individuals with SMA, structural brain abnormalities were more frequent in those with 2 *SMN2* copies (3/5, 60%) compared with 3 or 4 *SMN2* copies (4/10, 40% and 2/6, 33%, respectively) (OR 2.5, 95% CI 0.4–17.1). Structural brain abnormalities were also more frequent in individuals with SMA type I (3/4, 75%) compared with type II (3/9, 33%) and type III (3/8, 38%) (OR 5.5, 95% CI 0.7–51.0). The types of

Table 1 Participant Characteristics and Macrostructural Brain MRI Findings

	Controls N = 21	Patients with SMA N = 21	*p* Value
Participant characteristics			
Age at MRI (y), median (IQR)	14.7 (9.9–22.3)	14.4 (9.9–23.5)	0.990
Male, N (%)	14 (66.7)	14 (66.7)	1.000
Term birth, N (%)	21 (100.0)	20 (95.2)	1.000
Handedness			
Right-handed, N (%)	19 (90.5)	19 (90.5)	1.000
Left-handed, N (%)	2 (9.5)	2 (9.5)	
Macrostructural brain MRI findings			
Abnormal brain MRI, N (%)	2 (9.5)	9 (42.9)	0.032
Chiari I malformation, N (%)	0 (0.0)	1 (4.8)	
Choroid plexus xanthogranuloma, N (%)	0 (0.0)	1 (4.8)	
Developmental venous anomalies, N (%)	1 (4.8)	0 (0.0)	
Periventricular focal lesion, N (%)	0 (0.0)	1 (4.8)	
Periventricular nodular heterotopia, N (%)	0 (0.0)	1 (4.8)	
Supratentorial ventriculomegaly, N (%)	1 (4.8)	4 (19.0)	
Temporal fossa arachnoid cyst, N (%)	0 (0.0)	1 (4.8)	
T2 signal hyperintensity along posterior lateral ventricles, N (%)	0 (0.0)	1 (4.8)	
Widening of arachnoid spaces, N (%)	0 (0.0)	4 (19.0)	

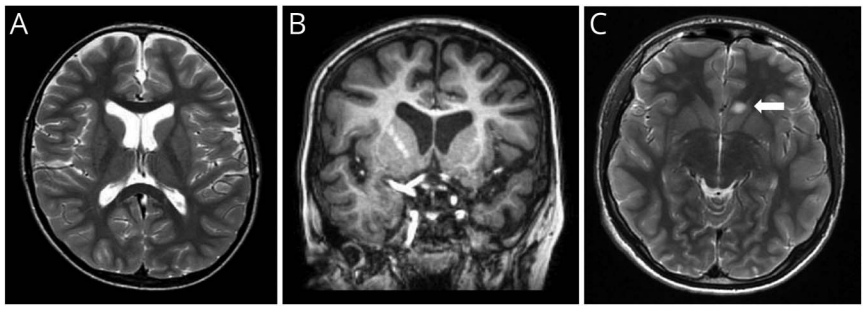
Abbreviations: IQR = interquartile range; SMA = spinal muscular atrophy.

Table 2 Characteristics of SMA Patients With and Without Macrostructural Brain Abnormalities

	All patients with SMA N = 21	Normal MRI N = 12	Abnormal MRI N = 9
Participant characteristics			
Age at MRI (y), median (IQR)	14.4 (9.9–23.5)	14.4 (10.2–21.7)	14.4 (8.9–31.8)
Male, N (%)	14 (66.7)	7 (58.4)	7 (77.8)
Age at symptom onset (y), median (IQR)	1.5 (0.5–3.0)	1.5 (0.6–3.0)	0.7 (0.1–2.0)
Age at treatment initiation (y), median (IQR)	11.8 (6.3–21.3)	13.5 (7.1–19.5)	8.5 (3.4–28.5)
SMA type, N (%)			
Type I	4 (19.0)	1 (8.3)	3 (33.3)
Type II	9 (42.9)	6 (50.0)	3 (33.3)
Type III	8 (38.1)	5 (41.7)	3 (33.3)
***SMN2* copy number, N (%)**			
Two copies	5 (23.8)	2 (16.7)	3 (33.3)
Three copies	10 (47.6)	6 (50.0)	4 (44.4)
Four copies	6 (28.6)	4 (33.3)	2 (22.2)
Disease-modifying therapy, N (%)			
Nusinersen	16 (76.2)	8 (66.7)	8 (88.9)
Risdiplam	5 (23.8)	4 (33.3)	1 (11.1)
Motor function			
Current best motor function, N (%)			
Head control	3 (14.3)	1 (8.3)	2 (22.2)
Sitting with support	3 (14.3)	2 (16.7)	1 (11.1)
Sitting independently	7 (33.3)	4 (33.3)	3 (33.3)
Walking with aid	3 (14.3)	2 (16.7)	1 (11.1)
Walking independently	5 (23.8)	3 (25.0)	2 (22.2)
HFMSE (score/66), median (IQR)	19.5 (4.5–50.0)	29.0 (4.0–52.0)	10.0 (3.0–42.5)
RULM (score/37), median (IQR)	27.0 (16.0–37.0)	32.5 (13.8–37.0)	26.0 (13.5–34.5)

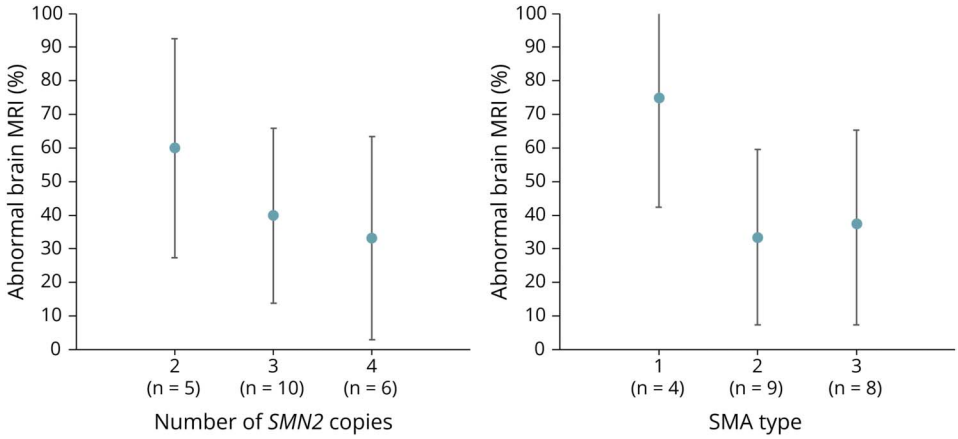
Abbreviations: HFMSE = Hammersmith Functional Motor Scale Expanded; IQR = interquartile range; RULM = Revised Upper Limb Module; SMA = spinal muscular atrophy; SMN = survival motor neuron.
All *p* values >0.05.

Figure 3 Macrostructural Abnormalities



Examples of structural brain abnormalities observed in patients with SMA. (A) Widening of the anterior arachnoid spaces and widening of the frontal horns of the bilateral lateral ventricles. (B) Asymmetric widening of the arachnoid spaces and widening of the supratentorial ventricular system. (C) Left frontal paraventricular focal lesion of hyperintense T2 signal.

Figure 4 Macrostructural Abnormalities by *SMN2* Copy Number and SMA Type



Rate of macrostructural brain abnormalities among patients with SMA, classified by (left) number of *SMN2* copies and (right) SMA type. Error bars represent the 95% confidence interval.

observed structural brain abnormalities classified based on SMA type are detailed in eTable 1.

Motor Function Scores

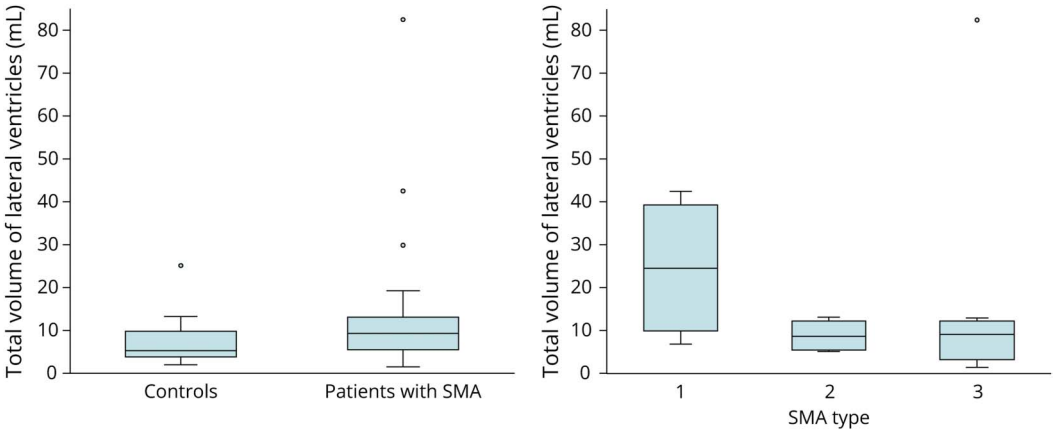
SMA patients with structural brain abnormalities had lower median HFMSE (10.0, IQR 3.0–42.5 vs 29.0, IQR 4.0–52.0; p = 0.456) and RULM scores (26.0, IQR 13.5–34.5 vs 32.5, IQR 13.8–37.0; p = 0.720) compared with those without, not reaching significance.

Ventricular Volume

The 5 participants reported to have qualitative ventriculomegaly on brain MRI had significantly larger volumes of the lateral ventricles (median 29.9 mL, IQR 22.2–62.5) compared with those without ventriculomegaly (median 6.4 mL, IQR 4.3–9.7; p < 0.001). In addition, as illustrated in Figure 5, patients with SMA (n = 21) had larger median ventricular volume than peer controls (n = 21) (9.3 mL, IQR 5.5–13.1 vs 5.3 mL, IQR 3.8–9.8; p = 0.034). Removing the outlier type III SMA patient with a history of prematurity and intraventricular hemorrhage and their matched control from analyses did not change this observation substantially. The patients with SMA (N = 20) had a median ventricular volume of 9.1 mL vs 5.3 mL for controls.

In the SMA group, individuals with type I SMA had larger median volumes of the lateral ventricles (24.6 mL, IQR 10.0–39.4) than individuals with type II (8.7 mL, IQR 5.5–12.3) or type III SMA (9.1 mL, IQR 3.3–12.2) (not reaching significance, with p = 0.081 for type I vs II or III). Similarly, individuals with 2 *SMN2* copies had larger median volumes of the lateral ventricles (19.3 mL, IQR 9.7–36.2)

Figure 5 Total Lateral Ventricular Volume



Total volume of the lateral ventricles for (left) peer controls and patients with SMA and (right) patients with SMA stratified by SMA type. The ventricular volumes were measured by MRI volumetry. The outlier type III SMA patient with a total lateral ventricular volume of 82.5 mL had no signs of hydrocephalus in the brain MRI study. They were born prematurely (29 + 5 weeks) and had evidence of intraventricular hemorrhage in the neonatal period with no known clinical sequelae.

than those with 3 copies (9.1 mL, IQR 6.6–12.3) or 4 copies (4.7 mL, IQR 2.6–28.1) (p = 0.050 for 2 vs 3 or 4 copies). However, we found no clear correlation between ventricular volume and motor scores (HFMSE p = 0.099, RULM p = 0.249).

Discussion

In our cohort, the odds of macrostructural brain abnormalities detected by MRI were 7 times higher in individuals with SMA than their normally developing peers. We identified 8 distinct types of structural brain abnormalities in patients with SMA, with the most prevalent being ventriculomegaly and widening of the arachnoid spaces. Among individuals with SMA, those with 2 *SMN2* copies and/or type I SMA had the highest rate of structural brain abnormalities and largest volume of the lateral ventricles. We observed no correlation between the frequency of structural changes and functional motor scores.

Our results and those of others found structural brain abnormalities to be more prominent in individuals with the most severe form of SMA. A recent study reported extensive white matter volume decreases in patients with type II and type III SMA relative to healthy controls.[16] The degeneration of the right postcentral gyrus was more severe in individuals with type II compared with type III SMA, as well as in those with lower HFMSE scores. However, another group found that the reduction in cerebellar volume (lobules VIIIB, IX, and X) exhibited by individuals with type III and IV SMA did not correlate with *SMN2* copy number nor SMA type.[14] Of interest, in our cohort, the frequency of abnormal brain MRI correlated with SMA type but did not correlate with HFMSE and RULM scores. The absence of an association between structural abnormalities and the severity of motor impairment could reflect a lack of sensitivity of these clinical tests. Alternatively, and more likely, it could indicate that structural brain abnormalities are more closely linked to genotype and/or early-life motor outcomes—factors that influence SMA type assignment—rather than long-term best motor function.

Our data suggest that the prevalence of structural abnormalities is not affected by the individual's age, or the number of years lived with SMA. In fact, the median age of SMA patients with normal brain MRI was the same as those with abnormal findings (14.4 years old). This is consistent with other studies reporting no correlation between patient age or disease duration and neuroimaging findings such as spinal cross-sectional area or cerebellar volume.[14,15] By contrast, previous studies have reported a significant correlation between motor cortex volumes and disease duration.[15]

The types of structural brain abnormalities we observed in the SMA population are similar to those previously reported in the literature. In this study, the most frequently structural brain abnormalities identified in patients with SMA included ventriculomegaly and widening of the arachnoid spaces, which together suggest cerebral atrophy. These results are consistent with published case reports and case series describing ventricular dilatation, sulcus widening, as well as diffuse atrophy and white matter reduction in individuals with SMA type 0 and I.[11-13] In addition, 1 patient with type II SMA in our cohort had evidence of T2 signal hyperintensity along the posterior contours of the lateral ventricles on brain MRI, a finding previously documented in patients with SMA types I and II.[13,18,19] Conversely, while several groups have reported corpus callosum abnormalities in patients with SMA such as tapering, hypoplasia, and dysplasia, all individuals with SMA in our cohort exhibited a normal corpus callosum.[11,13,19]

Nonetheless, similar structural brain abnormalities have also been documented in other neuromuscular disorders. Indeed, white matter hyperintense lesions, ventriculomegaly, and enlargement of subarachnoid spaces have been reported in patients with congenital muscular dystrophies, dystroglycanopathies, and myotonic dystrophies.[20] It is possible that structural brain abnormalities in SMA arise from substantially reduced SMN protein levels during a critical period of early brain development.[9,19] However, these overlapping findings between neuromuscular disorders raise the question whether restricted motor development in early life could instead be responsible for the alterations in brain architecture identified in patients with SMA.

Another plausible explanation is that the identified structural changes may not be exclusive to neuromuscular diseases but rather occur in the context of chronic hypoxia. Respiratory muscle weakness is a prominent feature of SMA, particularly in patients with the more severe types. Moreover, evidence from a mouse model of SMA demonstrated widespread tissue hypoxia and a cellular hypoxic response across multiple organs.[21] Chronic hypoxia resulting from conditions such as obstructive sleep apnea, chronic obstructive pulmonary disease, or high-altitude living has been linked to cognitive dysfunction and alterations in brain structure.[22] These structural changes include cortical atrophy and ventricular enlargement, similar to what we observed in patients with SMA.

Our study's cross-sectional design limits our ability to examine a temporal relationship between disease-modifying therapies and macrostructural brain abnormalities. A small number of hydrocephalus cases have been reported among patients with SMA treated with nusinersen, as well as a greater incidence overall compared with peers.[23] However, since hydrocephalus is more common in patients with SMA than in non-SMA controls, the association with nusinersen remains unclear.[23]

No participant in our cohort had evidence of hydrocephalus on brain MRI, and the ventricular enlargement observed in certain patients with SMA is likely ex vacuo as a consequence of encephalic volume loss. It is important to note that there was a considerable delay in starting disease-modifying therapies for patients with type I SMA in our cohort (median delay

of 2.9 years). As SMA becomes integrated into an increasing number of newborn screening programs, we anticipate earlier treatment initiation, potentially reducing the extent of observed atrophy and ventriculomegaly.

In clinical practice, ventriculomegaly is typically reported based on the radiologist's subjective assessment of images. In specific populations such as neonates, linear measurements such as the ventricular index, anterior horn width, and thalamo-occipital diameter are used to quantify ventricular dilatation.[24] More recently, some groups have adopted MRI volumetry for more precise measurements of ventricular volumes, although normative values are not well established. In our cohort, patients with SMA exhibited significantly greater median ventricular volumes than peer controls, and this was most pronounced in individuals with type I SMA or 2 *SMN2* copies. While we did not find prior studies evaluating ventricular volume in patients with SMA, our findings align with case series documenting marked ventricular enlargement in the most severe forms of SMA.[11,12]

The main strengths of our study include detailed image acquisition using 3T MRI scanners, facilitating the identification of more subtle structural abnormalities. In addition, all brain MRIs were interpreted by a single neuroradiologist to ensure consistency, and qualitative assessments of ventriculomegaly were validated through quantitative measurements of ventricular volume. Nonetheless, this study has important limitations. First, the relatively small size of our cohort and its clinical heterogeneity regarding SMA type, age, and treatment status reduced our statistical power and may affect the external generalizability of our results. Second, we unintentionally included 1 patient with a history of acquired brain disorder (intraventricular hemorrhage without clinical sequalae) that was missed prior to enrolment in this study. However, including this patient did not substantially alter our results. Third, we did not conduct volumetric analyses beyond ventricular volume, which could potentially offer further insights within our cohort. Finally, brain MRIs were acquired on 2 different scanners (Montreal and Calgary), although we had patients with SMA and age-matched peer controls for each scanner. Larger longitudinal studies are necessary to validate our results and further explore the intricate relationship between motor dysfunction, treatment, and structural brain alterations in SMA. Furthermore, emerging evidence of neurodevelopmental comorbidities in patients with SMA indicates potential differences in functional connectivity, alongside macrostructural changes, which were not evaluated in this study.[25]

Individuals with SMA have higher rates of macrostructural brain abnormalities than their normally developing peers, suggesting CNS involvement in SMA. Understanding changes in brain architecture may not only inform the development of adjunct therapies but also potentially provide guidance for rehabilitation strategies within the SMA population.

Study Funding

This study was funded by Muscular Dystrophy Canada.

Disclosure

E. Groulx-Boivin, A. Oliveira-Carneiro, H. Carlson, A. Floer, and A. Kirton report no disclosures relevant to the manuscript; J.K. Mah. received research grants from Biogen, Italfarmaco SpA, Novartis, NS Pharma, Pfizer, PTC Therapeutics, ReveraGen Biopharma, Roche, Sarepta Therapeutics, and the Alberta Children's Hospital Foundation; C. Saint-Martin reports no disclosures relevant to the manuscript; R. La Piana is a junior 1 research scholar of the Fonds de Recherche du Quebec - Santé, she received research funds from Roche Canada, consulting honoraria from Novoglia, and speaking honoraria from Novartis; M. Oskoui is a senior clinical research scholar of the Fonds de Recherche du Québec—Santé. Go to Neurology.org/NG for full disclosures.

Publication History

Received by *Neurology: Genetics* June 28, 2024. Accepted in final form August 26, 2024. Submitted and externally peer reviewed. The handling editor was Editor Stefan M. Pulst, MD, Dr med, FAAN.

Appendix Authors

Name	Location	Contribution
Emilie Groulx-Boivin, MD	Departments of Pediatrics and Neurology and Neurosurgery, Montreal Children's Hospital, McGill University, Montreal, Quebec, Canada	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Andrea Oliveira-Carneiro, MSc	Research Institute, McGill University Health Centre, Montreal, Quebec, Canada	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design
Helen Carlson, PhD	Alberta Children's Hospital Research Institute; Department of Pediatrics, Cumming School of Medicine, University of Calgary, Alberta, Canada	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data
Amalia Floer	Alberta Children's Hospital Research Institute; Department of Pediatrics, Cumming School of Medicine, University of Calgary, Alberta, Canada	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design
Adam Kirton, MD, MSc	Alberta Children's Hospital Research Institute; Department of Pediatrics, Cumming School of Medicine, University of Calgary, Alberta, Canada	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data
Jean Mah, MD, MSc	Alberta Children's Hospital Research Institute; Department of Pediatrics, Cumming School of Medicine, University of Calgary, Alberta, Canada	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design
Christine Saint-Martin, MD, MSc	Division of Pediatric Medical Imaging, Department of Radiology, Montreal Children's Hospital, Montreal, Quebec, Canada	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data

Appendix *(continued)*

Name	Location	Contribution
Roberta La Piana, MD, PhD	Department of Neurology and Neurosurgery, Montreal Neurological Institute; Department of Diagnostic Radiology, McGill University, Montreal, Quebec, Canada	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Maryam Oskoui, MD, MSc	Departments of Pediatrics and Neurology and Neurosurgery, Montreal Children's Hospital, McGill University; Research Institute, McGill University Health Centre, Montreal, Quebec, Canada	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

References

1. Verhaart IEC, Robertson A, Wilson IJ, et al. Prevalence, incidence and carrier frequency of 5q-linked spinal muscular atrophy - a literature review. *Orphanet J Rare Dis.* 2017;12(1):124. doi:10.1186/s13023-017-0671-8
2. Chen E, Dixon S, Naik R, et al. Early experiences of nusinersen for the treatment of spinal muscular atrophy: results from a large survey of patients and caregivers. *Muscle Nerve*. 2021;63(3):311-319. doi:10.1002/mus.27116
3. Yeo CJJ, Tizzano EF, Darras BT. Challenges and opportunities in spinal muscular atrophy therapeutics. *Lancet Neurol.* 2024;23(2):205-218. doi:10.1016/s1474-4422(23)00419-2
4. Battaglia G, Princivalle A, Forti F, Lizier C, Zeviani M. Expression of the SMN gene, the spinal muscular atrophy determining gene, in the mammalian central nervous system. *Hum Mol Genet.* 1997;6(11):1961-1971. doi:10.1093/hmg/6.11.1961
5. Tizzano EF, Cabot C, Baiget M. Cell-specific survival motor neuron gene expression during human development of the central nervous system: implications for the pathogenesis of spinal muscular atrophy. *Am J Pathol.* 1998;153(2):355-361. doi:10.1016/s0002-9440(10)65578-2
6. Ramos DM, d'Ydewalle C, Gabbeta V, et al. Age-dependent SMN expression in disease-relevant tissue and implications for SMA treatment. *J Clin Invest.* 2019;129(11):4817-4831. doi:10.1172/jci124120
7. Wishart TM, Huang JP, Murray LM, et al. SMN deficiency disrupts brain development in a mouse model of severe spinal muscular atrophy. *Hum Mol Genet.* 2010;19(21):4216-4228. doi:10.1093/hmg/ddq340
8. d'Errico P, Boido M, Piras A, et al. Selective vulnerability of spinal and cortical motor neuron subpopulations in delta7 SMA mice. *PLoS One.* 2013;8(12):e82654. doi:10.1371/journal.pone.0082654
9. Mugisha N, Oliveira-Carneiro A, Behlim T, Oskoui M. Brain magnetic resonance imaging (MRI) in spinal muscular atrophy: a scoping review. *J Neuromuscul Dis.* 2023;10(4):493-503. doi:10.3233/jnd-221567
10. Harding BN, Kariya S, Monani UR, et al. Spectrum of neuropathophysiology in spinal muscular atrophy type I. *J Neuropathol Exp Neurol.* 2015;74(1):15-24. doi:10.1097/nen.0000000000000144
11. Mendonça RH, Rocha AJ, Lozano-Arango A, et al. Severe brain involvement in 5q spinal muscular atrophy type 0. *Ann Neurol.* 2019;86(3):458-462. doi:10.1002/ana.25549
12. Maeda K, Chong PF, Yamashita F, et al. Global central nervous system atrophy in spinal muscular atrophy type 0. *Ann Neurol.* 2019;86(5):801-802. doi:10.1002/ana.25596
13. Oka A, Matsushita Y, Sakakihara Y, Momose T, Yanaginasawa M. Spinal muscular atrophy with oculomotor palsy, epilepsy, and cerebellar hypoperfusion. *Pediatr Neurol.* 1995;12(4):365-369. doi:10.1016/0887-8994(95)00058-n
14. de Borba FC, Querin G, França MC Jr., Pradat PF. Cerebellar degeneration in adult spinal muscular atrophy patients. *J Neurol.* 2020;267(9):2625-2631. doi:10.1007/s00415-020-09875-4
15. Querin G, El Mendili MM, Lenglet T, et al. The spinal and cerebral profile of adult spinal-muscular atrophy: a multimodal imaging study. *Neuroimage Clin.* 2019;21:101618. doi:10.1016/j.nicl.2018.101618
16. Shen W, Yan Z, Su S, et al. Gray and white matter abnormalities in children with type 2 and 3 SMA: a morphological assessment. *Eur J Pediatr.* 2024;183:1381-1388. doi:10.1007/s00431-023-05397-z
17. Rorden C, Karnath HO, Bonilha L. Improving lesion-symptom mapping. *J Cogn Neurosci.* 2007;19(7):1081-1088. doi:10.1162/jocn.2007.19.7.1081
18. Ito Y, Kumada S, Uchiyama A, et al. Thalamic lesions in a long-surviving child with spinal muscular atrophy type I: MRI and EEG findings. *Brain Dev.* 2004;26(1):53-56. doi:10.1016/s0387-7604(03)00075-5
19. Losito L, Gennaro L, Lucarelli E, Trabacca A. Brain MRI abnormalities in a child with spinal muscular atrophy type II. *Acta Neurol Belg.* 2021;121(6):1883-1885. doi:10.1007/s13760-020-01524-x
20. Angelini C, Pinzan E. Advances in imaging of brain abnormalities in neuromuscular disease. *Ther Adv Neurol Disord.* 2019;12:1756286419845567. doi:10.1177/1756286419845567
21. Hernandez-Gerez E, Dall'Angelo S, Collinson JM, Fleming IN, Parson SH. Widespread tissue hypoxia dysregulates cell and metabolic pathways in SMA. *Ann Clin Transl Neurol* 2020;7(9):1580-1593. doi:10.1002/acn3.51134
22. Wang X, Cui L, Ji X. Cognitive impairment caused by hypoxia: from clinical evidences to molecular mechanisms. *Metab Brain Dis.* 2022;37(1):51-66. doi:10.1007/s11011-021-00796-3
23. Viscidi E, Wang N, Juneja M, et al. The incidence of hydrocephalus among patients with and without spinal muscular atrophy (SMA): results from a US electronic health records study. *Orphanet J Rare Dis.* 2021;16(1):207. doi:10.1186/s13023-021-01822-4
24. Volpe JJ, Inder TE, Darras BT, et al. *Volpe's Neurology of the Newborn E-Book*. Elsevier Health Sciences; 2017.
25. Baranello G, Neurodevelopment in SMA Working Group. The emerging spectrum of neurodevelopmental comorbidities in early-onset spinal muscular atrophy. *Eur J Paediatr Neurol.* 2024;48:67-68. doi:10.1016/j.ejpn.2023.11.006