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COMMUNICATION

CLINICAL ANATOMY WILEY

Can volumetric analysis of the brain help diagnose isolated optic neuritis?

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Abstract

Isolated optic neuritis is a single episode inflammatory optic neuropathy. This condition, which affects the optimal function of the optic nerve, is not associated with neurological or systemic diseases. Our study aimed to compare patients with isolated optic neuritis and normal healthy individuals in terms of the cerebrum, cerebellum and hippocampus volumes by using the "volBrain Online MRI Brain Volumetry System" program. Persons diagnosed with isolated optic neuritis ($n = 16$) and persons without any disease ($n = 16$) were included in the study. VolBrain was used to process the MRI data and, the findings were compared with Mann–Whitney *U* test. Values with a *p*-value <0.05 were considered statistically significant. The cerebrum white matter volumes in the total brain and in the right–left hemispheres of the brain were statistically significantly lower in the optic neuritis group ($p = 0.029$; $p = 0.050$; $p = 0.029$, respectively). In the segmental cerebellum analysis, the left side lobule VIIIB, the total and right–left side lobule IX volumes were statistically significantly higher ($p = 0.022$; $p = 0.014$; $p = 0.029$; $p = 0.018$, respectively). In total, lobule I-II volume was statistically significantly lower in the optic neuritis group ($p = 0.046$). In the segmental hippocampus analysis, the right side CA2-CA3, the total and right–left side SR-SL-SM volumes were statistically significantly lower in the optic neuritis group ($p = 0.039$; $p = 0.050$; $p = 0.016$, respectively). There are neurodegenerative changes in brain volume in patients with isolated optic neuritis. Although volBrain alone is not sufficient to diagnose isolated optic neuritis, it provides quantitative data that can be used as a complementary diagnostic method.

KEYWORDS
automatic segmentation, brain atrophy, diagnostic imaging, isolated optic neuritis, volumetric analyses

1 | INTRODUCTION

The term optic neuritis (ON) is used to describe various conditions that affect the optimal function of the optic nerve (Guier & Stokkermans, 2020). The consensus on the systematic nosology for ON is still unclear. Toosy et al. proposed a widely used classification based on clinical features (Toosy et al., 2014). According to this classification, ON is divided into typical and atypical. Typical optic neuritis develops subacute, lasting hours or days. It is a clinical condition in which the complaint of pain during eye movements occurs together with reduced vision. Typical optic neuritis is isolated optic neuritis and optic neuritis associated with multiple sclerosis (MS). There are two subgroups of isolated optic neuritis: solitary and recurrent. Neither solitary nor recurrent isolated optic neuritis is associated with a systemic disease. Atypical optic neuritis is vision loss that does not recover within a few weeks. Atypical optic neuritis is related to some systemic disorders, such as

chronic recurrent inflammatory optic neuropathy (CRION), Neuromyelitis Optica (NMO), and sarcoidosis (Nakazawa et al., 2021; Wingerchuk et al., 2015). Due to the clinically overlapping features of typical and atypical ON, reliable biomarkers are required to distinguish between subgroups accurately (Sarkar et al., 2021).

Early determination of optic neuritis etiology is vital for timely and proper treatment. In addition, understanding the cause of optic neuritis provides information about the prognosis of the patient's vision loss, reveals future health risks, and allows for additional examination and treatments (Bennett, 2019). It is essential to determine an effective and early treatment strategy for optimal recovery in ON, elucidate the mechanisms that constitute the pathogenesis of the disease, and develop a rapid, accurate, and differential diagnosis strategy (De Lott et al., 2022; Koseoglu & Tutuncu, 2020).

In diagnosing optic neuritis, detailed patient history and comprehensive clinical evaluation are essential. To define various etiologic causes, neuroimaging, and laboratory (e.g., oligoclonal bands [OCB], aquaporin-4 [AQP4]-IgG, anti-myelin oligodendrocyte glycoprotein [MOG]-IgG) and tests of visual function (perimetry, evoked potentials, optical coherence tomography) is part of the diagnosis (Bennett, 2019).

Magnetic resonance imaging for the brain, orbit, and spine is indicated to diagnose conditions that cause ON and to differentiate the diagnostic criteria for MS, NMO (Phuljhele et al., 2021). Contrast-enhanced MR-T1 sequence is one of the most important ancillary tests as it can directly reveal optic nerve inflammation. Brain MRI scans are initially abnormal in approximately 45% of patients, increasing to approximately 77% as the disease progresses (Ramanathan et al., 2018).

In recent years, detailed analysis of brain volumes has become popular with automatic programs that analyze brain volume and segmentation (Manjon et al., 2022). Brain anatomy and disease progression are examined by morphometric analysis of different clinical groups with automatic programs (Akudjedu et al., 2018). Whole brain, white and gray matter, brainstem, cerebrospinal fluid (CSF), hippocampus, and cerebellum volumes can be determined using Voxel-Based Morphometry (Acer et al., 2018). Although studies use VBM in many neurological diseases, especially MS, studies on isolated optic neuritis are limited.

Our study aimed to determine whether there is a difference in the cerebrum, cerebellum, hippocampus, and subcortical structures by evaluating the patients diagnosed with isolated optic neuritis and normal healthy individuals using the "volBrain Online MRI Brain Volumetry System (http://volbrain.upv.es)" program.

2 | MATERIALS AND METHODS

2.1 | Participants

Ethical approval of the study was obtained from the university's ethics committee (approval number: 1318). Persons diagnosed with optic neuritis ($n = 16$, age range: 16–48) and persons without any disease ($n = 16$, age range: 24–47) were included in the study. While the mean age of the isolated optic neuritis patients was 33.18, the mean age of the control group was 36.68. Age distributions between the groups did not differ statistically significantly.

There were 61 patients diagnosed with optic neuritis in the University Hospital Neurology Clinic between 2010 and 2022. Patients with a history of neurological and autoimmune disorders, trauma or cancer, and demyelinating plaques detected in MRI were excluded by retrospective analysis. An isolated optic neuritis group was formed from 16 patients who had the first optic neuritis attack and did not have any other accompanying disease. Sixteen individuals who did not have any visual complaints underwent diagnostic MRI examinations and normal MRI findings and were randomly assigned to the control group of 250 patients between the exact dates.

2.2 | MRI protocol

The brain and subcortical structures of the individuals included in the study were scanned with 3 Tesla MRI (MRI Systems Achieva Release 3.2.3.1, Philips Medical Systems, Holland). T1-weighted three-dimensional volumetric TFE (turbo field echo) sequences were obtained with the following scanning variables: acquisition matrix = 240 × 190, flip angle = 8°, TE = 3 ms, TR = 6.4 ms, FOV = 240 mm^2, number of slices = 158 and slice thickness = 1.0 mm. The MR examination was performed with a head coil (8 or 32-channel SENSE; Philips Medical Systems).

2.3 | volBrain analysis

VolBrain [v.1.0, http://volbrain.upv.es], an online MRI brain volume measurement method, processes MRI data to calculate local concentration differences of brain tissues with VBM (Manjón & Coupé, 2016). VolBrain is free software, it gives fast results, and it does not need any additional processes such as installation and fitting (Akudjedu et al., 2018). VolBrain is a fully automated segmentation technique whose algorithm is based method on multi-atlas patch-based tag merge segmentation technology. Image files in sagittal 3D-T1 DICOM (Digital Imaging and Communications in Medicine) format were converted to NIFTI-1 (Neuroimaging Informatics Technology Initiative) format and uploaded to the volBrain system. Analysis results were reported in pdf and csv format after 10–15 min of processing time. Volumetric analysis was performed using HIPS 1.0 for the hippocampus and its segmentation, volBrain 1.0 for the cerebrum and subcortical structures, and CERES 1.0 for the cerebellum and its segments. The CERES 1.0 analysis is illustrated in Figure 1.

2.4 | Statistical analysis

The normal distribution of the parameters was evaluated with the Shapiro–Wilk test. The parameters were non-normally distributed. Therefore, the Mann–Whitney *U* test was applied. The Mann–Whitney

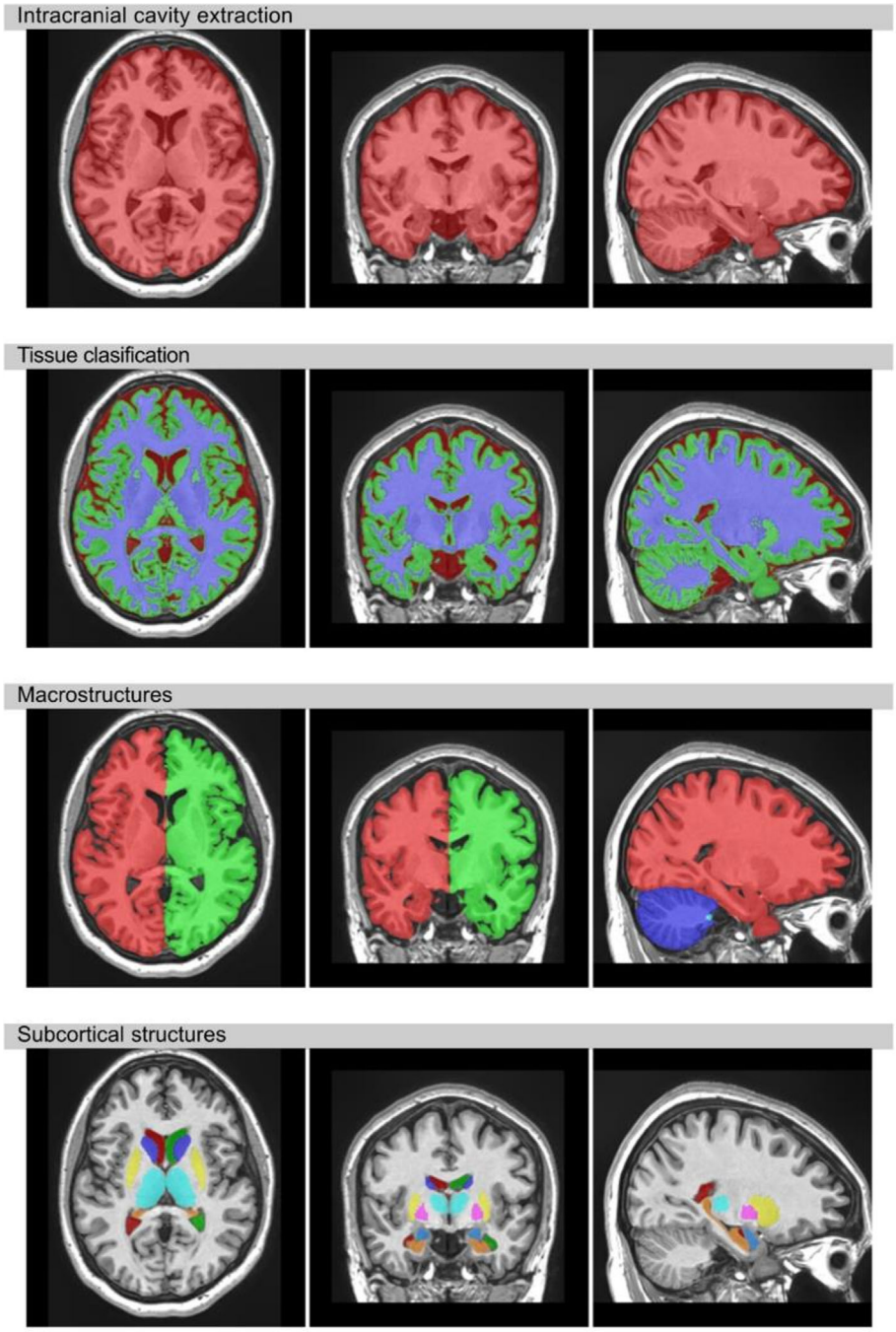

FIGURE 1 The image of cerebellum analysis of a 42 years old female patient with isolated optic neuritis. (In cortical thickness, a rainbow color map is given in absolute value (mm) to identify regional asymmetry visually.).

U test compared the volumes in optic neuritis and control groups. Values with a *p*-value <0.05 were considered statistically significant.

3 | RESULTS

3.1 | Comparison of control and optic neuritis group volumes

The comparison of cerebrum volumes in the optic neuritis group and control group is summarized in Figure 2. Cerebrum white matter in the total brain and in the right and left hemispheres of the brain were statistically significantly lower in the optic neuritis group ($p = 0.029$; $p = 0.050$; $p = 0.029$, respectively) (Figure 2A–C). Although the cerebrum gray matter (total, right and left hemispheres), tissue CSF, tissue brain, and brainstem volumes were not statistically significant in between groups ($p = 0.132$; $p = 0.132$; $p = 0.122$; $p = 0.546$; $p = 0.635$; $p = 0.243$, respectively).

The lateral ventricles, thalamus, amygdala and subcortical volumes in the hemispheres were measured, and summarized in Table 1. There was not any statistically significant difference between the groups.

The volume of the entire hippocampus and CA1, CA2-CA3, CA4-DG, SR-SL-SM and subiculum segments were evaluated with

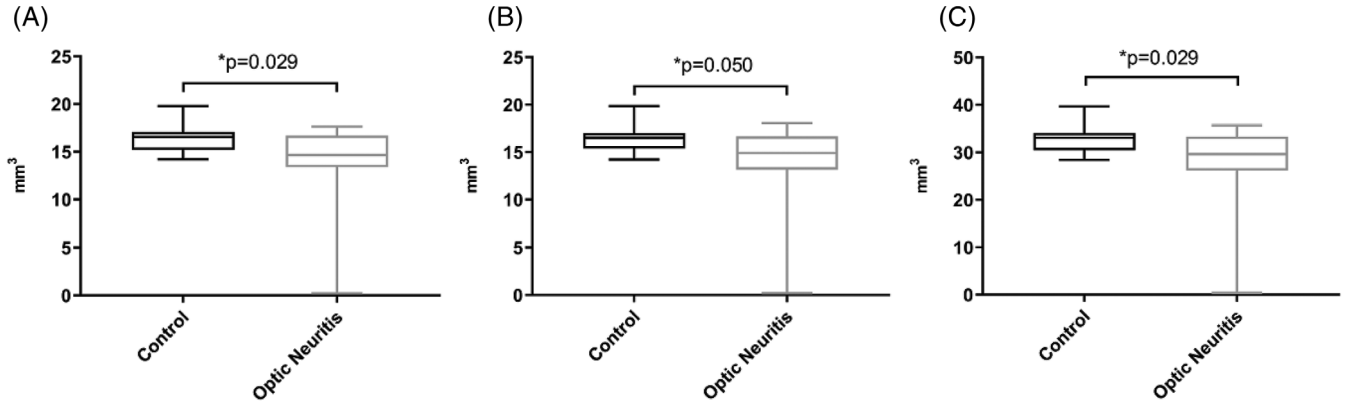

FIGURE 2 The comparison of cerebrum volumes in the optic neuritis group and control group. (A) cerebrum white matter in both side, (B) cerebrum white matter in the right side, (C) cerebrum white matter in the left side.

TABLE 1 Distribution of lateral ventricles, thalamus, amygdala and subcortical volumes in control and optic neuritis groups.

	Control	SEM	ON	SEM	*p*
Lateral ventricles total	1.01	0.16	0.61	0.10	0.073
Lateral ventricles right	0.48	0.08	0.30	0.05	0.050
Lateral ventricles left	0.53	0.08	0.31	0.05	0.065
Thalamus total	0.81	0.02	0.83	0.01	0.396
Thalamus right	0.40	0.01	0.41	0.00	0.762
Thalamus left	0.40	0.01	0.42	0.00	0.176
Amygdala total	0.10	0.00	0.09	0.00	0.215
Amygdala right	0.05	0.00	0.04	0.00	0.218
Amygdala left	0.05	0.00	0.04	0.00	0.106
Caudate total	0.51	0.01	0.50	0.02	0.925
Caudate right	0.26	0.00	0.25	0.00	0.924
Caudate left	0.25	0.00	0.25	0.01	0.820
Putamen total	0.57	0.01	0.56	0.02	0.835
Putamen right	0.28	0.01	0.27	0.01	0.790
Putamen left	0.29	0.00	0.28	0.01	0.909
Globus pallidus total	0.16	0.00	0.15	0.00	0.789
Globus pallidus right	0.08	0.00	0.07	0.00	0.466
Globus pallidus left	0.08	0.00	0.07	0.00	0.625
Nucleus accumbens total	0.04	0.00	0.04	0.00	0.664
Nucleus accumbens right	0.02	0.00	0.02	0.00	0.699
Nucleus accumbens left	0.02	0.00	0.02	0.00	0.699

HIPS 1.0 volume analysis. The right side CA2-CA3 and total and left side SR-SL-SM volumes were statistically significantly lower in the optic neuritis group ($p = 0.039$; $p = 0.050$; $p = 0.016$) (Figure 3A–C). The volumes of the total, right–left hippocampus and other segments were not statistically significant between of groups.

The lobule I-II, III, IV, V, VIIB, VIIIA, VIIIB, IX, X and lobule crus I, II segments were evaluated with CERES 1.0 volume analysis. These cerebellum segments are common parameters in the evaluation of both cerebellum gray matter and cerebellum total volumes. The lobule I-II volume in the both hemispheres were statistically significantly lower in the optic neuritis group ($p = 0.046$) (Figure 4A). The lobule VIIIB in the left hemisphere, lobule IX volumes in the total and right–left hemispheres were statistically significantly higher ($p = 0.022$; $p = 0.014$; $p = 0.029$; $p = 0.018$, respectively) (Figure 4B–E).

The lobule III gray matter volume in the left hemisphere of the cerebellum was statistically significantly lower in the optic neuritis group ($p = 0.008$) (Figure 4F). However, lobule VIIIB gray matter volume in the left hemisphere of the cerebellum and lobule IX gray matter volumes in the total and right–left hemispheres were statistically significantly higher in the optic neuritis group ($p = 0.029$; $p = 0.016$;

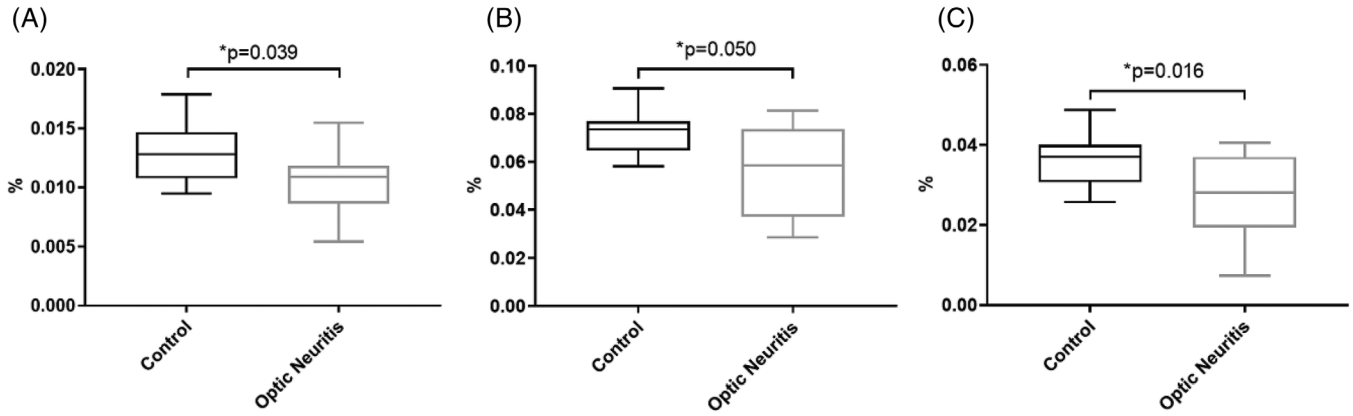

FIGURE 3 The comparison of hippocampus volumes in the optic neuritis group and control group. (A) CA2-CA3 in the right side, (B) SR-SL-SM in the total side (C) SR-SL-SM in the left side.

$p = 0.024$; $p = 0.012$, respectively) (Figure 4G–I, K). Other segments were not statistically significant between groups.

4 | DISCUSSION

A typical ON consists of 5%–25% isolated and recurrent optic neuritis subgroups. Isolated optic neuritis (ION) describes a single, ION episode without relapse. In addition, an MRI of the optic nerve shows signs of inflammation, but an MRI of the spinal cord is defined as standard in the ION (Petzold et al., 2010; Petzold et al., 2014).

Isolated optic neuritis is often attributed to clinically isolated syndrome (CIS). CIS is an ambiguous term, and it is generally used for the pre-MS clinical case (Ducloyer et al., 2021; Kale, 2016). A review article on the classification of optic neuritis was published by Ducloyer et al. in 2021. They suggested using the terms "isolated ON" or "possible MS" rather than using the term "CIS" based on MRI and CSF findings (Ducloyer et al., 2021). Confusion in the definition of optic neuritis based on clinical, radiological, and biological criteria has resulted in overlapping phenotypes. As a result, a single case of ON can be classified simultaneously and over time (Manjón & Coupé, 2016). Studies of isolated optic neuritis are limited in the literature.

MRI is necessary for excluding alternative diagnoses. MRI clearly shows optic nerve inflammation, revealing both damage and atrophy. Classical MRI signs are T2 (preferably with fat suppression) lesions with high signal intensity in the optic pathways (optic chiasm and optic nerve), and approximately 94% of patients have increased contrast T1-weighted images. Often there is swelling of the affected part of the optic nerve (Petzold, 2017; Petzold et al., 2013; Petzold & Plant, 2012).

Inflammation in optic neuritis causes neurodegeneration in visual pathways as well as anterograde (retina to cortex) and retrograde (cortex to the retina) transsynaptic functional changes (Davion et al., 2020). Atrophy of brain regions has been demonstrated in many neurodegenerative processes, including disease or senility (Author & Javadi, 2019; Coupé et al., 2017; Iliadou et al., 2022). Our study's strength was that patients with neurological, autoimmune disease, and trauma history and MRI findings of senile cerebral atrophy or demyelinated plaques were omitted. The reason for this exclusion was the investigation of brain volumetric differences in a pure isolated optic neuritis group.

A study using brain volume and DTI techniques, which are imaging techniques sensitive to neurodegeneration, aimed to evaluate whether early measurements can provide additional information about disease progression. Moreover, their results pointed out that brain volume measurements did not offer significant results for intergroup or correlation analyses (Gajamange et al., 2019). Kallenbach et al. conducted a study investigating signs of retinal atrophy with OCT and brain with MRI in a cohort of treatment-naive patients with monosymptomatic unilateral ON. They reported no atrophy in the total brain volume and gray and white matter volume (Kallenbach et al., 2011).

In our study, brain volumes were examined extensively. Total brain and gray matter volume in our study did not have results similar to those of Kallenbach et al.'s studies. However, in both, right–left side white matter volumes were atrophic in the optic neuritis group (Figure 2). Audin et al. conducted a study examining the location of anomalies using fundamental voxel analysis of gray matter magnetization transfer rate (MTR) maps. Their study reported that the bilateral visual cortex (BA17/18), left hippocampus, bilateral superior temporal gyrus, right lenticular nucleus, and right cerebellum showed lower MTR in the isolated optic neuritis group than in healthy controls. They did not report a significant difference in terms of gray matter percentage between patients and controls (Coupé et al., 2017). Similarly, our study found essential findings in the cerebellum and hippocampus. Our study method allowed for segmental examination of structures (Manjón & Coupé, 2016). As a result of segmental cerebellum analysis, the left side lobule VIIIB, the both, right–left side lobule IX and lobule IX gray matter, the left side lobule VIIIB gray matter volumes were higher in the optic neuritis group (Figure 4). These findings may suggest a compensatory mechanism. However, both side lobule I-II, the

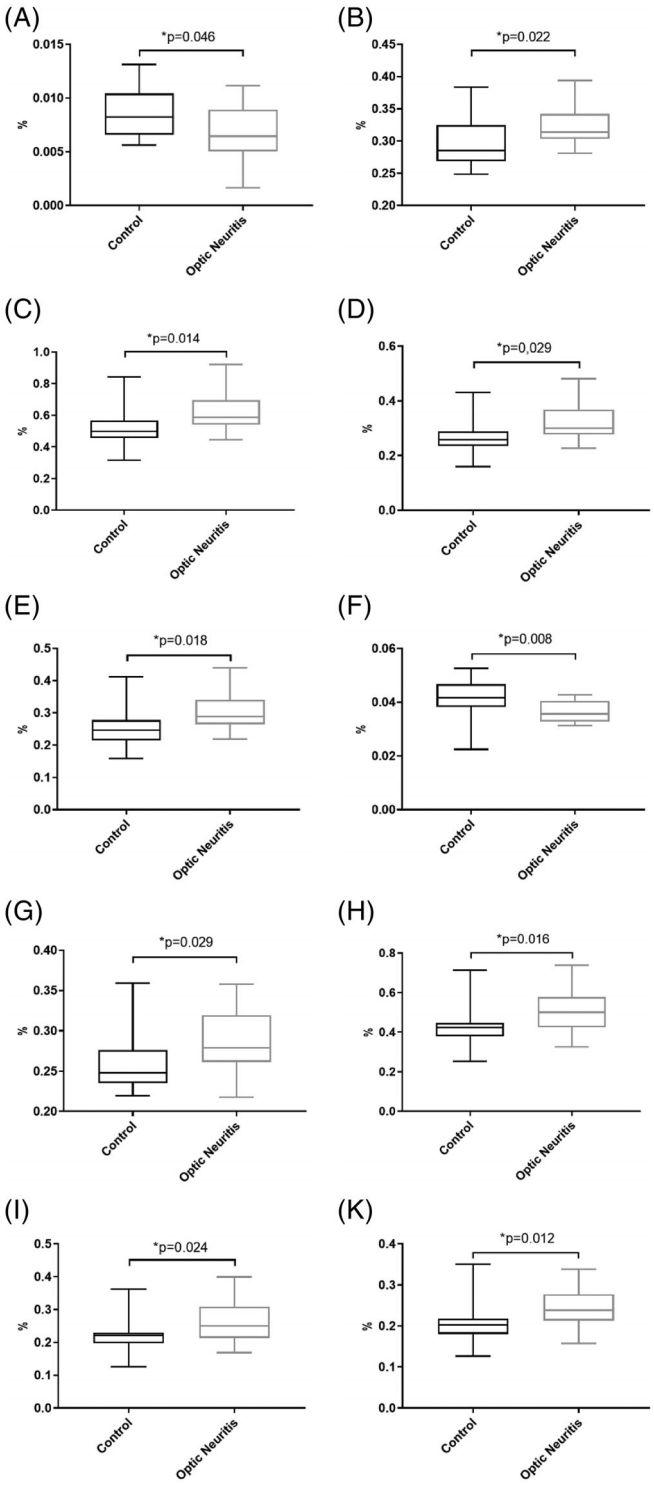

FIGURE 4 The comparison of cerebellum volumes in the optic neuritis group and control group. (A) lobule I-II in both sides, (B) lobule VIIIB in the left side, (C) lobule IX in the both side, (D) lobule IX in the right side, (E) lobule IX in the left side, (F) lobule III gray matter in the left side, (G) lobule VIIIB gray matter in the left side, (H) lobule IX gray matter in the total, (I) lobule IX gray matter in the right side, (K) lobule IX gray matter in the left side.

left side lobule III gray matter in segmental cerebellum analysis (Figure 4) and the right side CA2-CA3, both side and the left side SR-SL-SM volumes in segmental hippocampus analysis (Figure 3) were atrophic in patients. Therefore, the pathogenesis of ON and the cerebellum-hippocampus relationship require a detailed examination. Study based on a rodent model will help to shed light on this issue.

5 | CONCLUSION

In conclusion, brain atrophy can be detected in segmental volBrain analyses even in the acute phase in patients with isolated optic neuritis. Detecting the extent and localization of atrophy in the ION has clinical importance, and can provide descriptive quantitative data for sub-groups. However, volBrain is not sufficient to determine whether isolated cases of optic neuritis are precursors to MS. Holistic and detailed clinical investigations are required in patients with isolated optic neuritis.

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