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# Diagnostic and prognostic role of proton single-voxel spectroscopy (SVS) in non-lesional epilepsy pediatric patients: prospective controlled study

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## Abstract

**Background:** We aimed to verify the diagnostic and prognostic role of proton single-voxel spectroscopy (SVS) in children with non-lesional epilepsy and its add-on value to conventional MR. The prospective controlled study carried out on the epileptic patients who were regularly following in the pediatric neurology clinic in our university hospital, over the period from July 2017 to July 2018. It compared SVS findings (NAA/Cr, NAA/Cho, and NAA/Cho+Cr ratios) between the case (50 patients) and control group (20 children), between the cases with different seizures semiology and between the patients with intractable and non-intractable epilepsy.

**Results:** NAA/Cr ratio showed a significant difference between the patients with intractable and non-intractable epilepsy in the basal ganglia ( $P$  value 0.005) and white matter ( $P$  value 0.043) with cutoff values of 1.5 and 1.9 respectively. A significant difference of NAA/Cho ratio was found between generalized seizures cases and other seizures semiology in basal ganglia ( $P$  value 0.012) and cortex ( $P$  value  $<.001$ ). There was no significant difference between the patient and control groups or between generalized seizures cases and the control group.

**Conclusion:** Proton SVS has limited diagnostic value in non-lesional epilepsy pediatric patients, in differentiation between generalized seizures and other seizure types, but, it has a good prognostic role in predicting patients who will develop intractable epilepsy.

**Keywords:** MR spectroscopy, Single-voxel spectroscopy, Epilepsy, Non-lesional epilepsy

## Background

Epileptic seizures affect 1–2% of the population and 4% of children. Childhood epilepsy has a prevalence of approximately 0.5–0.8% and comprises a heterogeneous group of disorders, including a variety of epilepsy syndromes that range in severity from benign to progressive and catastrophic [1].

According to ILAE (International League Against Epilepsy) “2014”. Epilepsy is defined as a disease of the

brain characterized by any of the following conditions: (a) at least two unprovoked (or reflex) seizures occurring  $>24$  h apart. (b) One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years. (c) Diagnosis of an epilepsy syndrome [2].

Magnetic resonance imaging (MRI) plays a key role in the evaluation of pediatric patients with seizures and is considered important for the detection of epileptogenic lesions. However, magnetic resonance spectroscopy (MRS) is not as widely used for the evaluation of children with seizures and is not included in the ILAE

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recommendations for the management of infantile seizures again in 2015 [3].

Many authors studied the role of MRS in epilepsy, with temporal lobe epilepsy (TLE) had a great part of these works [4–8]. One study studied MRS in non-lesional insular cortex epilepsy. They used both single-voxel spectroscopy (SVS) and multi-voxel spectroscopy techniques [9]. However, to our knowledge, no studies were dedicated to study SVS in non-lesional epilepsy in pediatric age group (after advanced research using PMC, pub Med, Google scholar and research gate data base up to November 2019).

Some studies used clinical parameters like type of seizures, cause of epilepsy, family history of epilepsy, semiology of seizures as a predictive value of intractable seizures [10]. Others postulated genetic factors. Unfortunately, none of them was approved as a definite predictor of treatment failure [11].

The goal of this prospective study was to determine whether SVS had additional value in children with non-lesional epilepsy. We correlated our results with the clinical findings and patients’ response to therapy.

**Methods**

**Patients**

Our study was a prospective controlled study. It had been conducted on pediatric epileptic patients who were regularly following in the pediatric neurology clinic, in our university hospital. It was carried out over the

period from July 2017 to July 2018. The study sample included two groups; the case group (50 epileptic patients) and the control group (20 neurologically free children).

The inclusion criteria included: Children from 1 to 18 years old from both genders who were diagnosed with epilepsy—according to ILAE criteria [2]—and showed unremarkable conventional brain MRI non-lesional epilepsy).

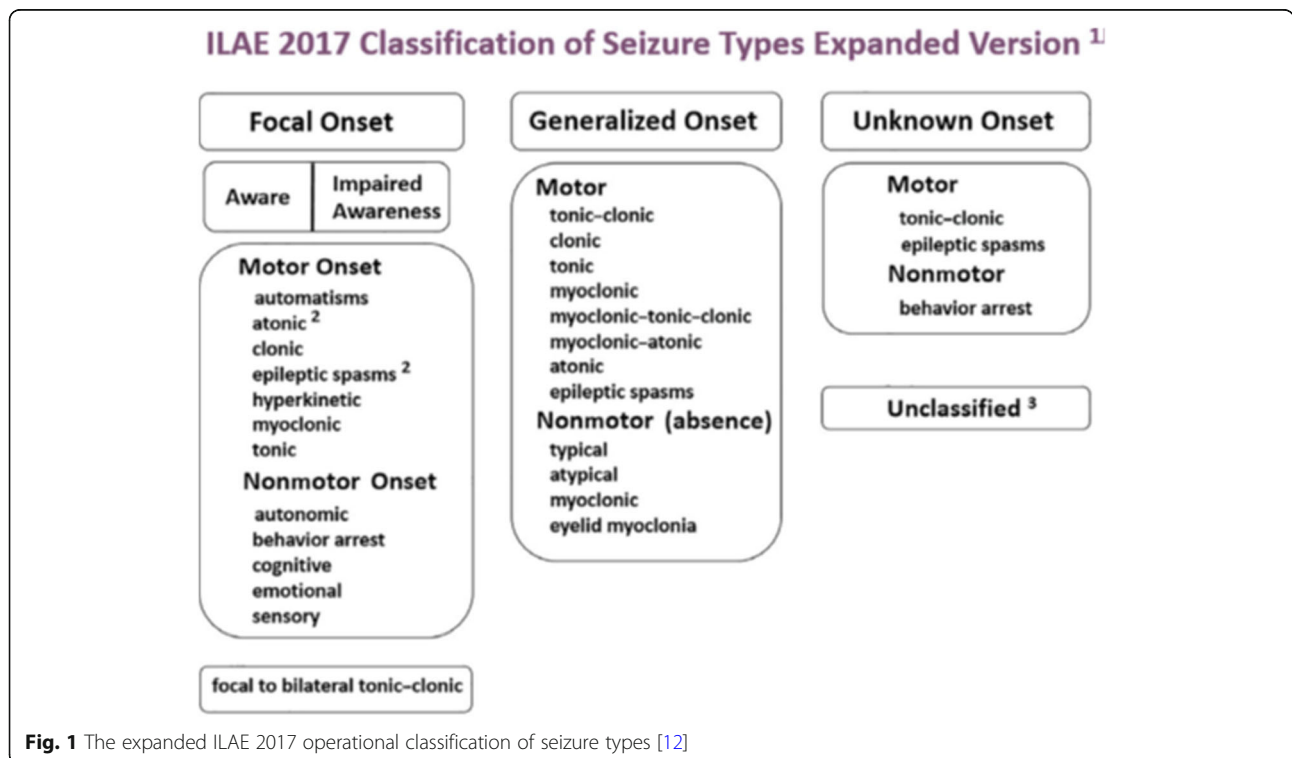
The exclusion criteria included; the presence of contraindications to MRI (such as pacemakers and cochlear implants) and epileptic children who had lesions in conventional brain MRI.

**Methodology**

Written consents for the study were obtained from the parents after a full explanation of the study procedures. The consents were obtained prior to the children’s enrollment in the study. The study protocol was approved by the Ethical Committees of our faculty.

The control group was chosen from other children presented to the pediatric outpatient clinic in our hospital after making sure that they were neurologically free. Their parents’s acceptance was requested and informed consent for the participation was taken.

*All the subjects in the cases group underwent the following:* Full history taking with special emphasis on perinatal history, developmental history, history of consanguinity, family history of epilepsy or febrile convulsion,



**Fig. 1** The expanded ILAE 2017 operational classification of seizure types [12]

semiology of the seizures, the age of onset, type of anti-epileptic drugs, response to treatment, seizure frequency, compliance to treatment.

Classification of seizure types according to the revised operational classification done by ILAE in 2017 (figure 1) [12].

According to the response to medical treatment, the cases group was divided into two sub-groups: non-intractable and intractable cases. The intractable (drug-resistant) epilepsy was defined as “failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom [13].

Physical examination (general and local): including a full neurological examination.

#### All the cases in each group were subjected to the following

**Conventional MRI:** MRI imaging was held using 1.5 T (Siemens, MAGNETOM Aera) machine, in MRI unit, radiology department, in our university hospital. The MR exam was done at least 2 weeks post last seizure attack to avoid the effect of postictal metabolic changes. The conventional MR study included the following sequences; axial and sagittal T1WIs SE (TE 8.9 ms, TR 450 ms), axial T2WIs TSE (TE 113 ms, TR 4490 ms), axial and coronal FLAIR (TE 107 ms, TR 9000 ms, TI 2500 and flip angle 150°), and coronal T1 inversion recovery images (TE 66 ms, TR 7000 ms, TI 350 and flip angle 160°).

**SVS:** voxels were placed at the left centrum semiovale, the left basal ganglia, and the midline parieto-occipital regions as representers of the white matter, deep grey matter, and cortical grey matter respectively. The examination was done using short echo time TE (30 ms) and long echo time TE (135 ms) with voxel size 2–5 ml (Fig. 2).

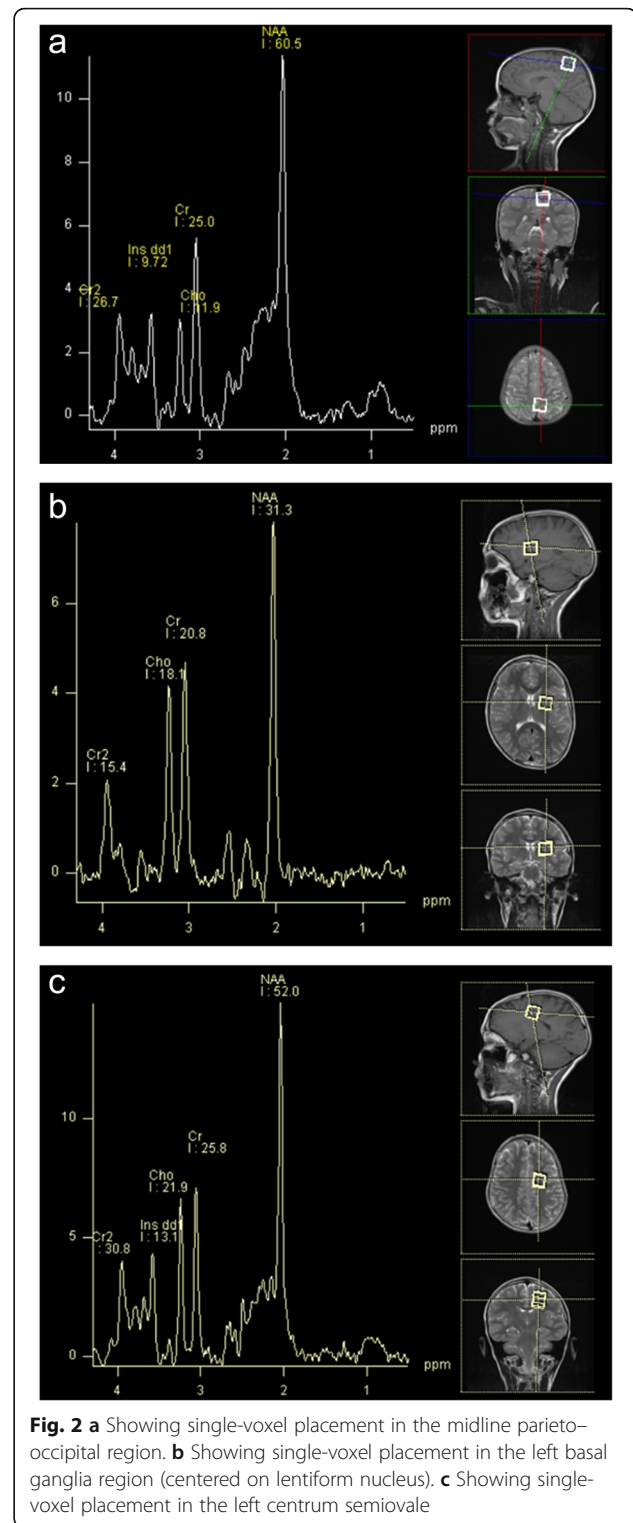
Both the MRI and SVS were done in the same setting. Children <7 years old and uncooperative ones were sedated either using chloral hydrate in a dose of 0.1 g/kg or using midazolam injection in a dose of 0.1 mg/kg together with propofol injection in a dose of 1 mg/kg followed by 0.5 mg/kg if necessary.

The integral values of various metabolite peaks were evaluated in every voxel. Three important metabolites resonance were identified: NAA at 2.02 ppm, Cr at 3.02 ppm, and Cho at 3.22 ppm.

The NAA/Cho ratio, the NAA/Cr ratio and the NAA/Cr+Cho ratios were calculated in the three different sites (the white matter, basal ganglia (Fig. 3), and cortical grey matter).

#### Statistical methods

- Data management and statistical analysis were done using SPSS vs.25. (IBM, Armonk, New York, United States).



**Fig. 2** a Showing single-voxel placement in the midline parieto-occipital region. b Showing single-voxel placement in the left basal ganglia region (centered on lentiform nucleus). c Showing single-voxel placement in the left centrum semiovale

- Numerical data was summarized as means and standard deviations. Categorical data was summarized as numbers and percentages.
- Comparisons between two groups were done using Mann Whitney U test for numerical data.

Categorical data was compared using chi-square test or Fisher's exact test if appropriate.

- Correlation analysis between different metabolites was done using Pearson's correlation. "r" is the correlation coefficient. It ranges from -1 to +1. -1 indicates a strong negative correlation, +1 indicates a strong positive correlation while 0 indicates no correlation.
- All P values were two-sided. P values less than 0.05 were considered significant.

## Results

Seventy persons were included in the current study (50 cases and 20 controls). Their epidemiological characters were illustrated in Table 1. There was no significant statistical difference between case and control groups regarding their age, sex, and family history of epilepsy.

According to the type of seizures, 44 (88%) cases presented with generalized seizures, while each of focal seizures, focal seizures with impaired awareness, and myoclonic seizures were presented by 2 (4%) cases. According to seizures control, 8 (16%) of cases presented with intractable epilepsy while other cases (42 cases "84%") were non-intractable.

No abnormal metabolite peaks were found in the short TE spectra of all cases group.

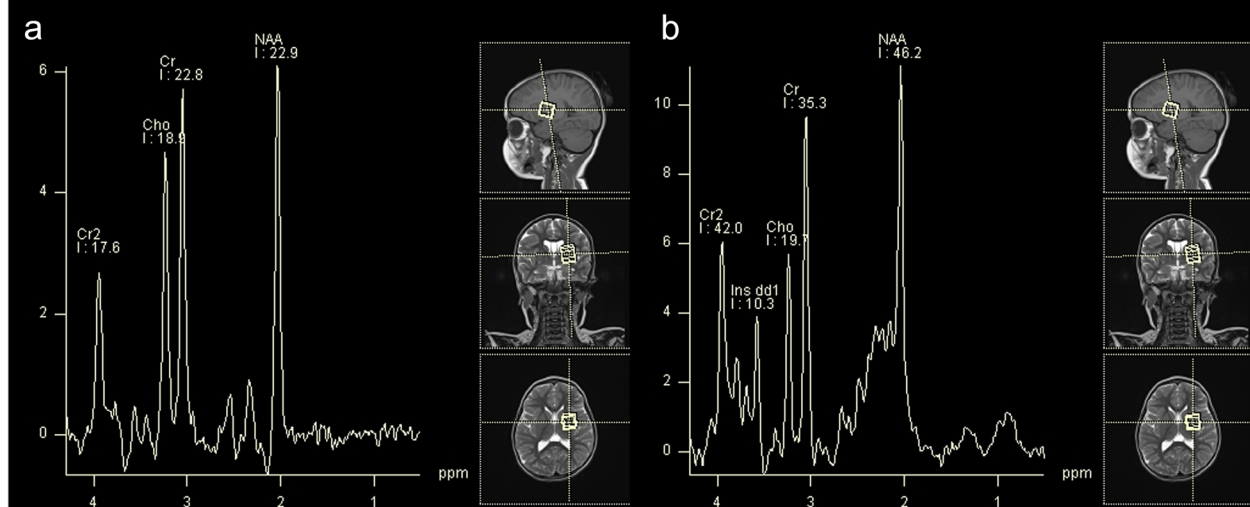
We did not find significant statistical differences between cases and control groups regarding the calculated NAA/Cho, NAA/Cr, and NAA/Cr+Cho ratios in the basal ganglia, white matter, and cortical grey matter (P values for NAA/Cho ratio were 0.268, 0.629, and 0.467, P values for NAA/Cr ratio were 0.281, 0.131, and 0.799

and P values for NAA/ Cho+Cr ratio were 0.852, 0.797, and 0.272 respectively).

There were no significant statistical differences between the cases with intractable seizures and those with non-intractable seizures regarding the calculated NAA/Cho ratio in basal ganglia, white matter, and cortical grey matter (P values 0.687, 0.254, and 0.482 respectively). However, the calculated NAA/Cr ratio showed statistically significant differences between the two groups in the basal ganglia and white matter. There was borderline significance found in cortical grey matter (Table 2).

Our results also showed a borderline significant statistical difference between cases with intractable seizures and those with non-intractable seizures regarding the calculated NAA/Cr+Cho ratio only in basal ganglia (P value 0.073), with no statistical difference noted in white matter and cortical grey matter (P values 0.345 and 0.297 respectively).

The present work revealed statistically significant differences between patients with generalized seizures and those with other seizure semiology regarding the calculated NAA/Cho ratio in basal ganglia (P value = 0.012) and cortical grey matter (P value <0.001), but no statistically significant differences noted in the white matter (P value = 0.812). In contrast, there was a statistically significant difference between the two groups regarding the calculated NAA/Cr ratio in white matter (P value = 0.03), yet no significant difference could be noted in the cortical grey matter and the basal ganglia (P values = 0.122 and 0.388 respectively). Also, we found statistically significant differences between the two groups regarding the calculated NAA/Cr+Cho ratio in cortical grey matter



**Fig. 3** Long (a) and short (b) TE SVS with voxel placed in the left lentiform nucleus, in a 5-years old female presented by intractable generalized seizures showing no abnormal peaks in the short TE spectrum. The long TE spectrum showed NAA/Cr=1, NAA/Cho=1.2, and NAA/Cho+Cr=0.54

**Table 1** General characteristics of case and control groups

		Cases (n = 50)	Controls (n = 20)	P value
<b>Age (years)</b>	Mean ± SD	5 ± 3	6 ± 4	0.937
<b>Gender</b>	Males n (%)	30 (60.0)	11 (55.0)	0.701
	Females n (%)	20 (40.0)	9 (45.0)	
<b>Family history of epilepsy</b>	Positive n (%)	2 (4.0)	0 (0.0)	1.0

( $P$  value = 0.016) with no significant difference noted in the white matter and basal ganglia ( $P$  values = 0.108 and 0.125 respectively).

The calculated NAA/Cr, NAA/Cho, and NAA/Cho+Cr ratios within the basal ganglia, white matter, and cortical grey matter showed no significant difference between the patients with generalized convulsions and the control group (Table 3).

ROC curve was calculated for NAA/Cr ratio in basal ganglia and gave cutoff value  $\leq 1.5$  for epileptic patients who could respond to medical treatment from those with intractable seizures, at maximum combined sensitivity and specificity of 100% and 62% respectively and area under the curve of 0.81; ( $P < 0.05$ ) (Fig. 4).

ROC curve was also done for the NAA/Cr ratio in white matter and found cutoff value  $\leq 1.9$  could differentiate epileptic children who will respond to treatment from those with intractable seizures, with best-combined sensitivity and specificity of 100% and 65% respectively. AUC = 0.758; ( $P < 0.05$ ) (Fig. 5).

## Discussion

In the current study, the case group included 50 epileptic patients, 30 males (60%), and 20 females (40%) with mean age of  $5 \pm 3$  years. The control group included 20 patients, 11 males (55%), and 9 females (45%) with mean age of  $6 \pm 4$  years. For most recent studies that reported gender, like the study conducted by Hawley et al. in 2015, gender-specific incidence in children was higher in males, although seldom statistically significant [14].

The case group included 8 patients (16%) with intractable epilepsy and 42 patients (84%) who were controlled with medication. This nearly agreed with the Dutch study by Arts et al. conducted as a 5-year follow-up study of epilepsy in childhood who found that 6–4% of children developed intractable epilepsy [15].

In the current study, the ILAE 2017 classification of seizure types was used. The most frequent type of seizures was generalized tonic-clonic seizures 88% followed by focal seizures with awareness which represented 4%, focal seizures with impaired awareness 4%, and myoclonic seizures which also represented 4%. This went with Farghaly et al., who conducted a study to determine the prevalence and clinical pattern of epilepsy among children and adolescents in upper Egypt. This study demonstrated generalized seizures as the most frequent type in epileptic children and adolescents [16].

In the present study, we used SVS technique, as it offered a good signal to noise and homogenous peaks within relatively short scan time [17]. We did not add a multivoxel technique in this study to avoid unnecessary prolongation of the exam time.

The quality of the signal received from metabolites in proton MRS directly depends on the physical parameters of the impulse sequence used, namely on Echo time (TE). In this study, we used short (30 ms) and long (135 ms) TE. As short TE allowed us to detect more metabolites especially myo-inositol and glutamates, As the change of their levels found to be related to poor outcome in some cases [18]. We also used long TE because the attenuation of the signal from the metabolites with shorter time of relaxation (TR), improves the signal-noise ratio of the main three metabolites (NAA, Cho, and Cr), and allowed better calculation of the ratios [19].

In their review article, Caruso et al. suggested one of two SVS protocols for the examination of the patients with non-lesional epilepsy. One protocol was to survey white matter, deep and cortical grey matter by using 3 voxels—using short TE of 35 ms—over the centrum semiovale, lentiform nuclei, and midline occipito-parietal cortex. Another protocol was using one voxel over the basal ganglia in order to save time [18]. In the present study, we went with Caruso's first protocol, we placed

**Table 2** NAA/Cr in basal ganglia, white matter, and grey matter according to seizures control

	Intractable (n = 8)	Non-intractable (n = 42)	P value
	Mean ± SD	Mean ± SD	
<b>In basal ganglion</b>	1.39 ± 0.12	1.67 ± 0.31	0.005*
<b>In white matter</b>	1.69 ± 0.21	1.89 ± 0.34	0.043*
<b>In grey matter</b>	1.67 ± 0.18	1.87 ± 0.29	0.06**

\*Significant, \*\*borderline significant

**Table 3** NAA/Cr, NAA/Cho, and NAA/Cho+Cr in basal ganglia, white matter, and cortical grey matter between the patients with generalized seizures and the control group

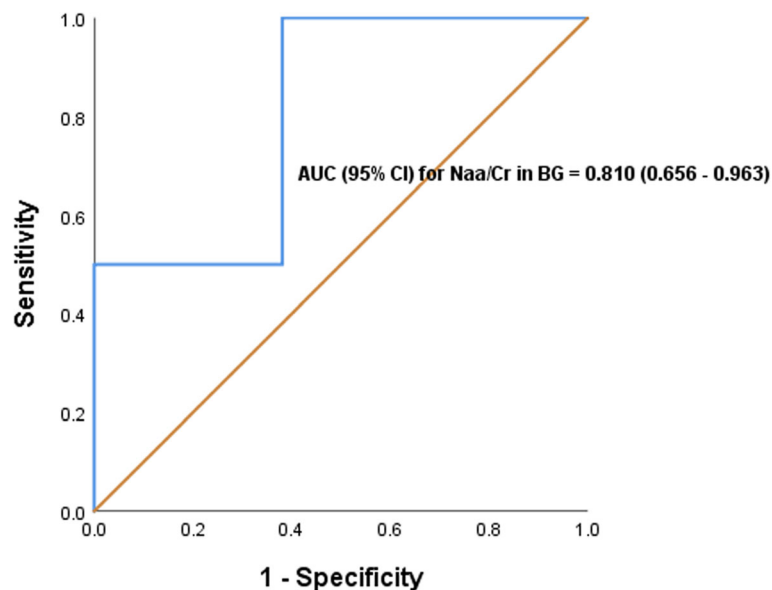
	Generalized seizures		Controls		P value
	Mean	±SD	Mean	±SD	
<b>NAA/Cho</b>					
Basal ganglion	2.33	0.56	2.24	0.49	0.482
White matter	1.91	0.37	1.86	0.25	0.586
Grey matter	2.81	0.79	2.79	1.23	0.901
<b>NAA/Cr</b>					
Basal ganglion	1.6	0.29	1.69	0.23	0.181
White matter	1.9	0.31	1.69	0.39	0.069
Grey matter	1.8	0.25	1.85	0.55	0.934
<b>NAA/Cr+cho</b>					
Basal ganglion	0.96	0.15	1.65	2	1
White matter	0.975	0.19	1.246	0.835	0.942
Grey matter	1.11	0.18	1.33	0.48	0.153

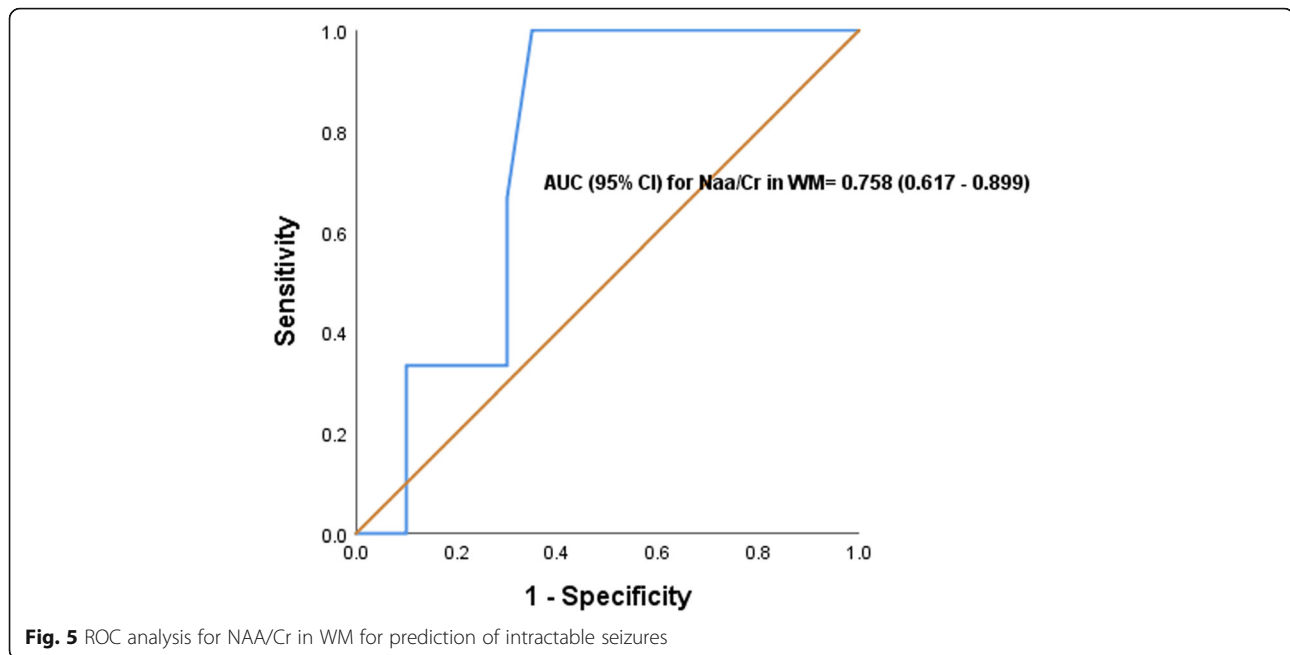
one voxel in the left centrum semiovale, one in the left lentiform nucleus, and one in the midline parieto-occipital region.

In the current study, the compared NAA/Cho, NAA/Cr, and NAA/Cr+Cho ratios between the cases and control groups (in the different sampled sites) showed no significant difference. These findings denied the value of these ratios in identifying the patients with non-lesional epilepsy. This went with Aitouche et al. who found that the measurement of absolute NAA and NAA/Cr ratio cannot differentiate between non-lesional insular epilepsy, extra insular epilepsy, and control groups [9].

On the other hand, the present results were in disagreement with Azab et al. who compared the NAA/Cr ratio between 40 TLE patients and 20 controls. They found a significant difference between the patients and control groups with a decreased level of the NAA/Cr ratio in the patient's group [8]. Also, Aun et al. conducted a study to evaluate the role of MRS in non-lesional TLE. They found that low NAA/Cho+Cr ratio allowed for lateralization of the epileptogenic focus in comparing both temporal lobes [7]. We did not go with Cendes et al. in their meta-analysis, as they found that proton MRS studies showed a focal reduction of NAA signal in patients with different forms of TLE, including those with normal magnetic resonance imaging (MRI), as well as extratemporal partial epilepsies [20]. This contradiction may be explained as this study was conducted on non-lesional epilepsy without identification of the epileptogenic focus, while other studies were conducted over epilepsy in which epileptogenic foci were detectable in conventional MRI, EEG, and/or fluoro-deoxyglucose-positron emission tomography (FDG-PET).

In comparing metabolite ratios between groups with intractable and non-intractable epilepsy, the NAA/Cr ratio showed a statistically significant difference in basal ganglia, white matter, and grey matter. We also found a borderline significant difference between NAA/Cr+Cho ratio in basal ganglia. Our results pointed to the value of NAA/Cr and NAA/Cr+Cho ratios as biomarkers that can predict the patient's response to treatment. This agreed with the study done by Campos et al. who demonstrated a significant reduction of NAA/Cr ratios in intractable TLE group compared with those who responded to the first antiepileptic drugs (AED) and to

**Fig. 4** ROC analysis for NAA/Cr in BG for prediction of intractable seizures



controls [21]. Also, this went with Briellmann et al. who found that NAA was significantly lower in refractory TLE patients compared with patients who responded to one anti-epileptic drugs [22].

This can be explained by the fact that NAA is considered a neuronal marker as it is found exclusively in neurons and their processes. In human brain spectra, NAA is reduced in the situations associated with neuronal loss or neuronal dysfunction. In patients with intractable seizures, the high frequency of breakthrough seizures, the more duration of the attacks, and the multiple antiepileptic drugs, all of these contribute to neuronal dysfunction [23].

In the present study, there were statistically significant differences between patients with generalized clonic seizures and those with other seizure semiology in NAA/Cho ratio in basal ganglia and grey matter, NAA/Cr ratio in white matter, and NAA/Cr+Cho ratio in the cortex. However, these ratios showed no significant difference between the patients with generalized seizures and the control group. This disagreed with Kasper et al. who used multi-voxel MRS to study the extent of local metabolic alterations in patients with idiopathic generalized epilepsy. They depended on the absolute values of the metabolites rather than ratios. They found a significant decrease ( $P < 0.05$ ) of tNAA in the cortical grey matter, thalamus, and basal ganglia, compared with the control group [24].

#### Limitation

- This study was done using magnetic field strength of 1.5 T. A higher-field strength of 3 T or more would yield a better spatial resolution and high SNR.

- Small sample size may reduce or bias the power of the results. Further studies with a larger sample size are necessary to extend these results.

#### Conclusion

SVS has limited diagnostic value in children with non-lesional epilepsy as it could differentiate between patients with generalized seizures and those with other seizure types, but it has a good prognostic tool in predicting patients who will develop intractable epilepsy.

#### Abbreviations

AED: Antiepileptic drugs; FLAIR: Fluid attenuation inversion recovery; ILAE: International League Against Epilepsy; MRI: Magnetic resonance imaging; MRS: Magnetic resonance spectroscopy; SV: Single-voxel spectroscopy; TE: Echo time; TI: Inversion time; TR: Repetition time; TLE: Temporal lobe epilepsy

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#### Authors' contributions

AD and OA carried up the clinical assessment of the epileptic patients and categorized the sample according to the seizures semiology and treatment response. MF supervised the MRS exams and interpreted their findings. All authors have read and approved the manuscript.

#### Funding

No funds were received for this study.

#### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

#### Competing interest

The authors declare that they have no competing interests in this section.

### Ethics approval and consent to participate

Written consents for the study were obtained from the parents after full explanation of the study procedures. The consents were obtained prior to the children's enrollment in the study. The study protocol was approved by the Ethical Committees of Benha faculty of medicine (The reference number of the ethical committee of Benha Faculty of Medicine is not available till now. I contacted the responsible person of the committee and she said that they are taking the steps nowadays to have a reference number in the international research board 'IRB', but they have not finished yet)

### Consent for publication

The parents of the cases were consented to publish the study data with the maintenance of full anonymity.

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