Original Article

Evaluation of Basal Ganglia in Paediatric Patients With Primary Nephrotic Syndrome by Brain Magnetic Resonance Histogram Analysis

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Abstract

Background: Primary nephrotic syndrome is an important cause of chronic renal failure in childhood. Important neuronal complications may develop during the disease. **Aims:** This study aims to demonstrate basal ganglia involvement in children with nephrotic syndrome by texture analysis. **Methods:** Brain MRI images of 22 paediatric patients with primary nephrotic syndrome and 40 healthy children of similar age groups were analysed. Brain MRI T2-weighted images were extracted from the thalamus, lentiform nucleus and nucleus caudatus and texture analysis was performed. **Results:** The images of 22 children with primary nephrotic syndrome and 40 children in the control group were evaluated. There were no notable distinctions identified in terms of age and gender between the patient and control groups (*P* value 0,410; 0,516, respectively). Accordingly, a significant difference was found between mean, 1.P, 10.P, 50.P, 90.P, 99.P values of histogram parameters obtained from thalamus (P values were 0.001; 0.000; 0.001; 0.002; 0.004; 0.009, respectively). A significant difference was found between mean, 1.P, 10.P, 50.P, 90.P, 99.P values of histogram parameters obtained from lentiform nuclei (*P* values were 0.031; 0.019; 0.006; 0.006; 0.003; 0.003; 0.001; 0.002, respectively). A significant difference was found between the mean, 1.P, 10.P, 50.P, 90.P, 99.P values of the histogram parameters obtained from the nucleus caudatus (*P* values 0,002; 0,005; 0,002; 0,002; 0,002; 0,003; 0,003, respectively). **Conclusion:** Texture analysis may be helpful in demonstrating brain parenchymal involvement in paediatric patients with primary nephrotic syndrome by showing changes that are not recognised on conventional images.

Keywords: *Magnetic resonance, nephrotic syndrome, texture analysis*

Introduction

Primary nephrotic syndrome (PNS) is one of the most common triggers of chronic kidney disease in childhood. It is characterised by symptoms such as protein loss, low albumin levels, fluid accumulation in the body and high cholesterol levels. The risk of infection includes various complications such as kidney damage, cardiovascular problems, bone mineral loss and neurological diseases.[1]

Low albumin levels can lead to a decrease in osmotic pressure and leakage of body fluids into tissues. This can affect the blood-brain barrier in the brain, leading to the development of oedema. Brain oedema can lead to increased intracranial pressure and associated neurological symptoms.[2]

Nephrotic syndrome can increase the tendency for blood clotting, which can increase the risk of clot formation in the brain vessels and thromboembolic events. Blood clots can damage brain tissue and increase the risk of stroke. Furthermore, <>nephrotic syndrome is associated with inflammation, which can

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affect brain health. Inflammation can damage cells in the brain and cause changes in neurological function.

Intracranial haemorrhage, Posterior Reversible Encephalopathy Syndrome (PRES), thromboembolic and ischaemic events are possible complications of nephrotic syndrome. Demonstration of brain parenchymal involvement by imaging modalities before these complications occur may be life-saving. We can recognise subtle structural changes in brain MRI images with texture analysis (TA). Lately, this method has gained extensive usage for the non-invasive quantitative evaluation of various pathological conditions. Texture analysis enables the retrieval of grey level intensity, pixel position, and the configuration and interconnection between voxel intensities from medical images.[3,4]

Radiomic features are commonly categorised into conventional, first-order, and second-order features. Given TA's capacity to unveil microstructural changes that may go unnoticed by the naked eye, numerous studies have explored its clinical relevance.[5-9] In this study, we investigated the potential role of MRI-based TA in predicting the severity of brain damage in paediatric patients with primary nephrotic syndrome.

Subjects and Methods

In our study, From March 2018 to May 2023, 22 children with primary nephrotic syndrome and 40 children without significant intracranial findings on brain MRI were retrospectively evaluated.

The revised MRI protocol included the following imaging sequences in the axial plane: T1-weighted spin-echo (TR/TE: 530–590/15–30 ms), T2-weighted turbo spin-echo (TR/TE: 4800–5680/100–120 ms), fluid-attenuated inversion recovery turbo spin-echo (TR/TE: 10500/130 ms; inversion time: 2850 ms) and diffusion-weighted imaging (TR/TE: 3100–3400/89 ms; b-value: 1000 s/mm2).

Texture analysis

Texture features were calculated on two-dimensional sectional images using 'qMaZda v4.6'.[10] The study of textural features in the basal ganglia, thalami and nucleus caudate head was initiated by M.D., a radiologist with 10 years of experience. Axial plane images obtained from T2W sequences were transferred in Digital Imaging and Communications in Medicine format from the medical database to qMaZda for the definition of regions of interest (ROIs). To ensure uniformity, gray levels were adjusted to 128 (7 bits). Automatic application of intensity rescaling values occurred within the range of mean ± 3 standard deviations (SDs). Pixels initially surpassing or falling below mean ± 3 SDs were normalised to mean ± 3 SDs. Following this, voxel values in three directions (X: 0.7 mm, Y: 0.5 mm, Z: 1 mm) were established based on their mean ± 3 SDs. Manual delineation of bilateral ROIs for texture analysis (TA) was performed for the basal ganglia, thalamus and head of nuclei caudati in each sequence on axial two-dimensional images [Figure 1].

Histogram parameters such as mean, variance, skewness, kurtosis, 1st percentile (P), 10th P, 50th P, 90th P and 99th P were calculated for each patient and control group over the areas identified in the head of the thalamus, lentiform nucleus and nucleus caudatus and evaluated separately for each case.

Ethical approval

In our study, which was approved by the Harran University Medical Ethics Committee with the decision dated 11.12.2023 and numbered 23.23.32, the ethical rules in the Declaration of Helsinki were complied with.

Statistical analysis

Statistical analyses were performed using SPSS version 22.0 (IBM Inc, Armonk, NY, USA). The normal distribution of numerical data was assessed through a comprehensive examination of Kolmogrov–Smirnov and Shapiro–Wilk tests. Descriptive statistics were used to express the results of the study; the mean ± standard deviation was applied for numerical data fitting the normal distribution, and the median with minimum-maximum values was applied for numerical data not fitting the normal distribution. Independent-student test and Mann–Whitney U test were used for intergroup measurements. *P* values less than 0.05 were considered significant.

Results

The images of 22 children with primary nephrotic syndrome and 40 children in the control group were

Table 1: Histogram parameters and comparison of images obtained from thalamus in patients and control group

	NF (*n*=22)	Control (*n*=40)	*P*
Mean	80.7±11.4	90.5±10.33	0.001[a]
Variance	46.91±16.4	42.3±14.3	0.26[a]
Skewness	-0.19(-0.3-0.15)	-0.05(-0.01-0.12	0.09[b]
Kurtosis	-0.47(-0.025-0.82	-0.51(-0.01—0.65)	0.063[b]
1.P	68.14±10.6	77.85±9.4	0.000[a]
10.P	72.8±10.9	82.8±9.9	0.001[a]
50.P	81±11.5	90±10.8	0.002[a]
90.P	90.5±12.7	99.6±10.7	0.004[a]
99.P	96.5±12	104±10.9	0.009[a]

[a]Independent samples *t* test. [b]Mann–Whitney *U* test. NF: Primer Nephrotic Syndrome

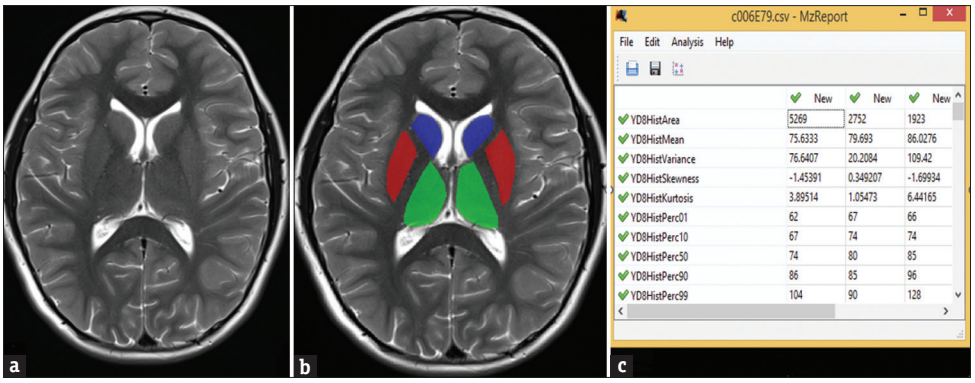

Figure 1: 12-year-old male patient with primary nephrotic syndrome. (a) Ventricular level on T2-weighted axial brain MRI image. (b) Two-dimensional segmentation of the thalamus (green), lentiform nucleus (red) and head of the nucleus caudatus (blue) from the same level using qMazda V.6 software. (c) Quantitative values of the histogram parameters of the area determined in image B.

Table 2: Histogram parameters and comparison of images obtained from lentiform nucleus in patients and control group

	NF (*n*=22)	Control (*n*=40)	*P*
Mean	88.5±11.05	95.8±8.853	0.003[a]
Variance	20.6±7.09	25.05±11.8	0.110[a]
Skewness	-0.08(-0.51-0.21)	-0.09(-0.31-0.32)	0.330[b]
kurtosis	-0.429(-0.21-0.32)	-0.51(-0.23-0.38)	0.901[b]
1.P	78.77±11.86	85.9±8.9	0.019[a]
10.P	82.8±11.26	90.18±8.73	0.006[a]
50.P	88.2±10.8	96.1±8.74	0.003[a]
90.P	94.5±11.5	102±9	0.001[a]
99.P	98.5±12	107±9.97	0.002[a]

[a]Independent samples *t* test. [b]Mann–Whitney *U* test. NF: Primer Nephrotic Syndrome

Table 3: Histogram parameters and comparison of the images obtained from the head section of the nucleus caudatus in the patient and control groups

	NF (*n*=22)	Control (*n*=40)	*P*
Mean	96.5±11.3	105±8.93	0.002[a]
Variance	24.36±19.3	22.35±8.55	0.573[a]
Skewness	0.144(-0.01-0.32)	0.24(-0.1-0.38)	0.300[b]
Kurtosis	0.609±1.95	0.301±1.23	0.545[b]
1.P	86.3±11.66	94.13±8.96	0.005[a]
10.P	91.09±11.43	99.55±9.10	0.002[a]
50.P	97.14±11.47	105.85±8.88	0.002[a]
90.P	102.2±11.28	111.3±8.8	0.003[a]
99.P	107±11.73	115±9.166	0.003[a]

[a]Independent samples *t* test. [b]Mann–Whitney *U* test. NF: Primer Nephrotic Syndrome

evaluated. While 13 of the children diagnosed with primary nephrotic syndrome were boys and 9 were girls, the control group consisted of 25 boys and 15 girls. The mean age of the children in the patient group was 9.5 ± 3.05 years, while the mean age of the control group was 9.1 ± 2.95 years. No significant difference was found between the patient and control groups in terms of age and gender (*P* value 0,410; 0,516, respectively).

In the brain MRI images of the patient and control groups, histogram analyses were performed from thalamus, lentiform nucleus and nucleus caudatus. Accordingly, a significant difference was found between mean, 1.P, 10.P, 50.P, 90.P, 99.*P* values of histogram parameters obtained from thalamus (*P* values were 0.001; 0.000; 0.001; 0.002; 0.004; 0.009, respectively) [Table 1].

A significant difference was found between mean, 1.P, 10.P, 50.P, 90.P, 99.P values of histogram parameters obtained from lentiform nuclei (*P* values were 0.031; 0.019; 0.006; 0.006; 0.003; 0.003; 0.001; 0.002, respectively) [Table 2].

A significant difference was found between the mean, 1.P, 10.P, 50.P, 90.P, 99.P values of the histogram parameters obtained from the head section of the nucleus caudatus (*P* values 0,002; 0,005; 0,002; 0,002; 0,002; 0,003; 0,003, respectively) [Table 3].

Discussion

In our study, significant differences were found in many histogram parameters in the texture analysis obtained from the thalamus, lentiform nucleus and head section of the nucleus caudatus in brain MRI images compared to the control group. In the literature, texture analyses have been performed for brain involvement in many diseases,[11-15] but this is the first study on brain involvement in children with primary nephrotic syndrome.

Quantitative imaging features can be derived from MRI-based TA, encompassing a variety of characteristics. The first-order statistical feature, often referred to as a histogram, involves the distribution of voxel densities within the Region of Interest (ROI). This distribution is based on fundamental properties such as skewness, kurtosis, entropy and energy of grey-level density. Based on the TA results of the patient and control groups in our study, it is thought that these differences are an indicator

of heterogeneity in the brain parenchyma in patients.[14] It is known that the brain tissue of paediatric patients with primary nephrotic syndrome may be affected through many mechanisms.[16,17] As a result, all these mechanisms can damage the brain in a wide range from intracranial haemorrhage to brain atrophia in the chronic period.[16]

Cerebral ischaemia, thromboembolism, PRES and intracranial haemorrhage are life-threatening developments in nephrotic syndrome. Undoubtedly, these complications are the result of an ongoing process. Conventional imaging modalities such as CT and MRI are not used to detect brain parenchymal involvement. However, especially in the early period, invisible grey tone differences are overlooked. For this purpose, the parameters called radiomics obtained by TA are nowadays helpful.[18,19]

Matsuda-Abedini *et al*. demonstrated the change in the arrangement of fibres in the white matter in children with chronic kidney disease with diffusion tracto radiography.[12] This finding is compatible with the results obtained in our study.

The statistical contrast in radiomics between the patient and control groups highlights the heterogeneity present in the brain parenchyma. Considering the possible vascular origins of cognitive impairments in this demographic, both our study and related findings underscore the necessity for future investigations probing the association between white matter imaging alterations and neurocognitive function in children with chronic kidney disease.

Uremic encephalopathy can manifest in individuals with chronic renal failure. The underlying mechanism involves inflammation of the brain parenchyma triggered by elevated amine-derived molecules. This leads to the disruption of the blood-brain barrier, ultimately causing oedema.[20] Kidney damage has the potential to activate cytokines that traverse the blood-brain barrier or stimulate other messengers, leading to neuronal dysfunction. Both case reports and human studies have documented various biochemical alterations in acute and chronic uremic encephalopathy. These changes encompass disruptions in water transport and cerebral oedema, disturbances in the blood-brain barrier and alterations in cerebral metabolism.[21] These changes in the brain parenchyma may not be detected on conventional MRI, especially in the early stages. TA helps in this regard by showing parenchymal heterogeneity at the micro level. Ruizhu *et al*. reported that histogram analysis would be useful in the demonstration of hypoglycaemic encephalopathy in the neonatal period.[22] In our study, we also noticed changes in the measurements at many basal ganglion levels which may indicate parenchymal damage.

Conclusions

This study draws attention to the importance of brain health in the care of children with primary nephrotic syndrome. The importance of TA in the prediction of important complications that may occur in the follow-up of these patients is emphasised. It is expected that further research on this topic in the future will further improve the brain health of children with primary nephrotic syndrome.

Ethical approval: This study was approved by the Harran University Medical Ethics Committee with the decision dated 11.12.2023 and numbered 23.23.32.

Study limitations

Our study has several limitations. Firstly, our study was conducted retrospectively. Due to the rarity of the diagnosis of primary nephrotic syndrome, the number of our patient group is small. Since TA is a current issue, there was no standard for the extraction of brain MRI images, but we tried to obtain images in accordance with the literature.[14,23,24]

Authors contributions

Concept-Design: MD; Literature review: M.D, S.O; Data collection: S.O; Writing-review-revision: M.D.

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Conflicts of interest

There are no conflicts of interest.

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