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Encephalatrophy and anti-N-methyl-D-aspartate receptor encephalitis

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Abstract

Objective: This study aims to find whether there are differences of clinical and laboratory features between anti-NMDAR encephalitis patients with and without brain atrophy. We also compare brain atrophy scale in anti-NMDAR positive patients with and without teratomas.

Methods: Brain atrophy scales of 82 patients with anti-NMDAR encephalitis were measured with the median temporal lobe atrophy (MTA) scale and the global cortical atrophy (GCA) scale. They were divided into two groups by brain atrophy status. In addition, 48 female patients with

anti-NMDAR encephalitis were divided into two groups with or without teratomas. Percentages of patients with brain atrophy were compared between these two groups.

Results: 33 (40.2%) patients had brain atrophy. The GCA (+) group had higher percentage of patients with status epilepticus ($p<0.001$) than GCA (-) group and the MTA (+) group had higher percentage of patients with memory deficits ($p < 0.001$) than MTA (-) group. Higher percentages of severe infections were found in GCA(+) and MTA (+) groups than those in GCA(-) and MTA (-) groups ($p=0.01$ and $p = 0.002$, respectively). The percentage of patients needing ventilatory support was higher in MTA (+) group than that in MTA (-) group ($p=0.015$). The modified Rankin Scale (mRS) scores of GCA(+) and MTA (+) groups were significantly higher when compared with GCA(-) and MTA (-) groups both at day one ($p<0.001$ and $p=0.001$, respectively) and at discharge ($p<0.001$ and $p = 0.02$, respectively). Patients in GCA (+) group had higher median length of hospital stay than those in GCA (-) group ($p<0.001$). The median onset-to-MR time of GCA(+) group was higher than that of GCA(-) group ($p=0.034$). Percentage of patients with limited response to treatment was higher in GCA (+) group than that in GCA(-) group ($p<0.001$). The median 25 hydroxyvitamin D3 level was lower in the GCA (+) group than that in GCA(-) group ($p=0.001$). Anti-NMDAR positive female patients with ovarian teratomas had higher percentage of

GCA(+) than thoes without ovarian teratomas (P=0.006).

Conclusions: Brain atrophy are not uncommon in patients with anti-NMDAR encephalitis. MTA and GCA may be associated with severity and prognosis of anti-NMDAR encephalitis.

Key words: Brain atrophy; anti-NMDAR encephalitis; GCA; MTA

1. Introduction

Anti-N-methyl- D -aspartate receptor (anti-NMDAR) encephalitis is a form of inflammatory encephalopathies in association with antibodies (immunoglobulin G) against the GluN1 subunit of the NMDAR. It predominantly affects young women with or without ovarian teratomas [1-3].

A variety of magnetic resonance imaging (MRI) findings have been reported in patients with anti-NMDAR encephalitis [2, 4-6]. However, few stuies focus on the brain atrophy in anti-N-methyl-D-aspartate receptor encephalitis. Iizuka et al found that cerebellar atrophy was irreversible and associated with poor outcome in patients with anti-N-methyl-D-aspartate receptor encephalitis [7]. However, This study based on only 15 patients. Further studies are needed to confirm the clinical association between brain atrophy and anti-N-methyl-D-aspartate receptor encephalitis.

This study aims to find whether there are differences of clinical and laboratory features between anti-NMDAR encephalitis patients with and without brain atrophy.

2. Methods

2. 1. Study population

Our database comprised 82 patients with anti-NMDAR encephalitis who were admitted from March 2014 to December 2018 in the department of neurology of the Third Affiliated Hospital of Sun Yat-sen University. Anti-NMDAR encephalitis was diagnosed in the presence of a core syndrome of limbic encephalitis (psychiatric symptoms, seizures, conscious disturbance and memory deficits) and detection of IgG antibodies against NMDAR [8]. And it is important to carefully exclude relevant differential diagnoses. Gender, age, modified Rankin Scale (mRS) and clinical manifestations were recorded. All patients underwent routine abdominal and pelvic ultrasound. And a pelvic computed tomography (CT) scan or magnetic resonance imaging (MRI) scan was performed when an ovarian teratoma was suspected. Treatments included first-line immunotherapy, second-line immunotherapy and tumour removal. First-line immunotherapy included the use of steroids, intravenous immunoglobulins or plasma exchange alone or combined. Second-line immunotherapy included rituximab, azathioprine or cyclophosphamide treatment alone or combined. The initial treatment

was recorded as a failure if no sustained improvement occurred within 1 month of initiation of immunotherapy or tumour removal, and if the mRS score remained at 4 or higher.

2.2. Detection of autoantibodies

After obtaining informed consent, cerebrospinal fluid (CSF) was collected from patients prior to treatment with methylprednisolone and other immunotherapies. The CSF sample was used for routine analysis and autoantibodies. Antibodies against NMDAR were tested by indirect immunofluorescence assay using commercial sampling kits (EUROIMMUN Medizinische Labordiagnostika, Lübeck, Germany).

2.3. Magnetic resonance imaging (MRI) and visual rating scales

Brain MRI scans were performed at 3.0 Tesla (Discovery MR750, GE Healthcare, Milwaukee, WI, USA). The slice thickness of the axial scans was 5 mm. Conventional MRI protocols were applied to all patients: T2-weighted (4392-5658/88.8-106 ms, TR/TE), T1-fluid-attenuated inversion recovery (FLAIR) (1782.6-1925.4/19.2-24.6 ms, TR/TE) and T2 FLAIR (8,400-8800/139.4-151.4 ms, TR/TE) for brain MRI.

Brain atrophy was measured with the median temporal lobe atrophy (MTA) scale based on T1-weigthed images and the global cortical atrophy (GCA) scale based on the T2-flair images as detailed before [9, 10]. The MTA scale was developed in 1992 by Scheltens et al., evaluating the choroid fissure, the temporal horn of the lateral ventricles

and the height of the hippocampus on a scale of 0 – 4 where a higher score means more atrophy in the region (table1) [9]. We evaluated severity of GCA according to Pasquier and co-workers on a 4-point rating scale ((0 = no atrophy; 1=mild GCA, sulcal opening peripherally; 2=moderate GCA, widening along the length of the sulci; 3=severe GCA, gyral thinning [10]. A neurologist and a neuroradiologist independently read all MRIs, blinded to clinical data.

2.4. Statistics analyses

All statistical analyses were conducted by using the SPSS 13.0 package for Windows (SPSS Inc, Chicago, IL, USA). Continuous data were presented as the mean ± standard deviation or median (range). Continuous data were compared by Student's t-test or the Mann Whitney U test. Nominal variables were analyzed using the chi-square test or Fisher's exact test.

3. Results

3.1. Baseline demographics and clinical characteristics among patients with anti-N-methyl- D -aspartate receptor encephalitis

Baseline demographics and clinical characteristics of patients with anti-N-methyl-D-aspartate receptor encephalitis were summarized in Table 2. The patients enrolled included 34 males (41.5%) and 48 females (58.5%) with ages ranging from 3 to 64 years. Among them, 58 patients (70.7%) were older than 18 years, 18 patients (22.0%) had a tumor, 52

patients (63.4%) had epileptic seizures, 64 patients (78.0%) had psychiatric symptoms, 43 patients (52.4%) had conscious disturbance, 35 patients (42.7%) had memory deficits and 33 patients (40.2%) had brain atrophy. The median MRS score was 4 (range, 1-5) at day one and 1 (range, 0-5) at discharge. The median length of hospital stay was 27.5 (range, 5-111). The median onset-to-MRI time was 42 (range, 2-1464). 80 patients (97.6%) received first-line treatment, 38 (46.3%) received combined first-line and second-line treatment, and 17 (20.7%) received tumour removal treatment.

3.2. Clinical correlation between anti-NMDAR encephalitis patients with and without brain atrophy

As shown in Table 3, patients with anti-NMDAR encephalitis were divided into two groups based on MTA and GCA scale. The GCA (+) group had higher percentage of female patients than that in GCA(-) group ($p=0.029$). No significant difference was found for median age and percentage of patients older than 18 years. As for the clinical presentation at onset, the GCA (+) group had higher percentage of patients with status epilepticus ($p<0.001$) than GCA (-) group and the MTA (+) group had higher percentage of patients with memory deficits ($p < 0.001$) than MTA (-) group. No significant difference was found for psychiatric symptoms and conscious disturbance. Higher percentages of severe infections were found in GCA(+) and MTA (+) groups than those in GCA(-) and MTA (-)

groups (p=0.01 and p = 0.002, respectively). The percentage of patients needing ventilatory support was higher in MTA (+) group than that in MTA (-) group (p=0.015). The modified Rankin Scale (mRS) scores of GCA(+) and MTA (+) groups were significantly higher when compared with GCA(-) and MTA (-) groups both at day one ($p<0.001$ and p=0.001, respectively) and at discharge ($p<0.001$ and p=0.02, respectively). Patients in GCA (+) group had higher median length of hospital stay than those in GCA (-) group ($p<0.001$). The median onset-to-MR time of GCA(+) group was higher than that of GCA(-) group (p=0.034). Percentage of patients with limited response to treatment was higher in GCA (+) group than that in GCA(-) group ($p<0.001$). As for laboratory test results, the median 25 hydroxyvitamin D3 level was lower in the GCA (+) group than that in GCA(-) group (p=0.001). There was no difference in percentage of patients receiving first line combined with second line treatment, CSF abnormalities, median antibody titers, median vitamin B1 level, median vitamin B2 level, median vitamin B6 level, median vitamin B12 level and mean folic acid level between patients with and without brain atrophy.

3.3. Comparison of brain atrophy in anti-NMDAR positive female patients with and without teratomas

Among the anti-NMDAR positive 48 female patients, 17 patients had ovarian teratoma and 31 patients were non-tumor associated. And we

found that anti-NMDAR positive female patients with ovarian teratomas had higher percentage of GCA (+) and higher median mRS score both at day one and at discharge than thoese without ovarian teratomas (P=0.006, p=0.037 and P=0.0033, respectively). The mean folic acid level of anti-NMDAR positive female patients with teratomas was lower than that of patients without teratomas (p=0.024). There was no difference in mean age, percentage of patients with MTA (+), percentage of status epilepticus, percentage of severe infections, median vitamin B1 level, median vitamin B2 level, median vitamin B6 level, median vitamin B12 level and median 25 hydroxyvitamin D3 level between the two groups.

4. Discussion

This study focused on the characteristics of anti-NMDAR encephalitis patients with brain atrophy. Previous studies demonstrated grey matter atrophy in patients with multiple sclerosis and neuromyelitis optical [11]. In multiple sclerosis, deep grey matter has been recognised as a crucial component of the disease and has been associated with disability [12]. In neuromyelitis optical, hippocampal volume is the main MRI predictor of cognition [13]. However, little is known about brain atrophy in anti-NMDAR encephalitis. In this study, more than one third had brain atrophy on plain MRI films measured with MTA scale and GCA scale in total 82 patients with anti-NMDAR encephalitis. This result demonstrated that brain atrophy were not uncommon in patients with anti-NMDAR

encephalitis. Medial temporal lobe atrophy as assessed by MTA was observed in 14.1% of patientson at least 1side and this finding is consistent with that in a previous study [14].

We found the GCA (+) group had higher percentage of female patients. This result may due to that all patients with teratoma were female in our study and we found that anti-NMDAR positive female patients with ovarian teratomas were more likely to have GCA than thoes without teratomas.

For clinical symptoms, we found that the MTA (+) group had higher percentage of patients with memory deficits than MTA (-) group. MTA-scale was usually used to assess degree of hippocampus atrophy on plain MRI films. A previous study demonstrated that the degree of MTA was significantly correlated with scores on memory tests, which was consistent with our finding [9].

We found that the median onset-to-MR time of the GCA (+) group was 60 which was higher than that of the GCA (-) group. A previous study demonstrated that brain atrophy in anti-NMDAR encephalitis started 1 to 2 month after symptom onset, which was consistent with our finding [7].

We also found that the modified Rankin Scale (mRS) scores of MTA (+) groups were significantly higher when compared with MTA (-) groups. A previous literature indicated that left hippocampal volume could predict disease severity [15] which was consistent with that in our

study. Also higher mRS scores were observed in patients with GCA. Patients with GCA were more likely to have limited response to treatment, need ventilatory support and had higher median length of hospital stay. The findings suggested that MTA and GCA may be associated with severity and prognosis of anti-NMDAR encephalitis. Lizuka et al reported several patients with anti-NMDAR encephalitis developed diffuse cerebral atrophy who had severe dyskinesias and they slowly recovered 3 to 4 years after symptom onset. Also, their brain atrophy were reversible [16]. So further studies are needed to confirm the association between long-term MRI changes and clinical outcome of patients with anti-NMDAR encephalitis.

The mechanisms of brain atrophy in anti-NMDAR encephalitis remain largely unknown. In this study we found that patients with brain atrophy had higher percentages of status epilepticus, severe infection and lower 25 hydroxyvitamin D3 level. According to previous studies, these factors may be associated with brain atrophy [17-19].

Previous studies indicated that an ovarian tumor could be found in approximately 26.9% to 44.2% of female patients with anti-NMDAR encephalitis [5, 20, 21] which was consistent with our finding (35.4%). We found that anti-NMDAR positive patients with ovarian teratomas were more likely to have GCA than patients without ovarian teratomas. We also found that patients with teratomas had higher mRS scores which

was consistent with the result in a previous literature [21]. Patients with a teratoma develop more robust immune responses than those without a tumour [22] and tend to present more severe neurological conditions [21]. In additon, we found that patients with teratomas had lower level of folic acid. A previous study conducted by Snowdon et al showed that low serum folate was strongly associated with atrophy of the cerebral cortex [23], though the mechanism remains to be determined.

5. Limitations and conclusions

There are some limitations in this study: (a) because we only enrolled patients with anti-NMDAR encephalitis, our conclusions may not be applied to patients with other types of autoimmune encephalitis; (b) bias is inevitable in retrospective studies; (c) we did not perform follow up of MR changes in this study.

In summary, this study confirmed that brain atrophy was not uncommon in patients with anti-NMDAR encephalitis. MTA and GCA may be associated with severity and prognosis of anti-NMDAR encephalitis. Also we found that anti-NMDAR positive patients with ovarian teratomas were more likely to have GCA than patients without ovarian teratomas. The exact mechanism of brain atrophy in anti-NMDAR encephalitis need further study.

Ethics approval and consent to participate

This research was approved by the ethics committee of the Third

Affiliated Hospital of Sun Yat-sen University.

Consent for publication

All participants involved in this study provided written informed consent.

Data availability statements

The datasets analysed during the current study available from the corresponding author on reasonable request.

Competing interests

None.

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Authors' contributions

Yinyao Lin: design of the work; Mengyan Hu and Haiyan Li: the acquisition, analysis; Sanxin Liu and Xuejiao Men: interpretation of data; Yilong Shan and Sha Tan: have drafted the work; Xuehong Huang and Zhengqi Lu: substantively revised it.

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Not applicable

Authors' information

None additional authors' information were showed.

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Table 1 Scoring according to the Scheltens MTA scale

MTA score	Width of the choroid fissure	Width of the temporal horn	Height of Hippocampal formation
0	N	N	N
1	↑	N	N
2	↑ ↑	↑	↓
3	↑ ↑ ↑	↑ ↑	↓ ↓
4	↑ ↑ ↑	↑ ↑ ↑	↓ ↓ ↓

Reproduced from Scheltens et al., 1992 (9).

MTA, medial temporal lobe atrophy.

Table 2 Baseline characteristics of anti-NMDAR encephalitis patients

Characteristics	Anti-NMDAR encephalitis
	N=82
F/M, n	48/34
Age (y, median, range)	22.5 (3, 64)
Patients with age≥18 years, n (%)	58 (70.7)
Tumour comorbidity (n, %)	18 (22.0)
ovarian teratoma	17 (20.7)
Colon carcinoma	1 (1.2)
Clinical presentation at onset, n (%)	
Epileptic seizures	52 (63.4)
Behavioral and psychiatric disturbances	64 (78.0)
Conscious disturbance	43 (52.4)
memory deficits	35 (42.7)
Patients with encephalatrophy, n (%)	33 (40.2)
Patients with GCA positive on MRI	30 (36.6)
Patients with MTA (one side/both sides) positive on MRI	12 (14.6)
mRS score at day one (median, range)	4 (1, 5)
mRS score at discharge (median, range)	1 (0, 5)
Length of hospital stay (median, range)	27.5 (5, 111)
Onset-to-MRI time (median, range)	42 (2, 1464)
Treatment (n, %)	
First line treatment	80 (97.6)
First line combined with second line treatment	38 (46.3)
Tumour removal	17 (20.7)
CSF abnormalities, n (%)	55 (67.1)
Antibody titers (median, range)	1:32 (1:1, 1:320)

NMDAR, N-methyl-d-aspartate receptor; F, female; M, male; y, year; GCA, global cortical atrophy; MTA, temporal lobe atrophy ; mRS, modified Rankin score; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging

Table 3 Comparison of clinical features in anti-NMDAR encephalitis patients with and without encephalatrophy

	GCA (+)	GCA (-)	P	MTA (+)	MTA (-)	P
	N=28	N=54		N=12	N=70	
F/M, n	21/7	27/27	0.029	6/6	42/28	0.516
Age (y, median, range)	26 (12, 64)	21.5 (3, 50)	0.057	22 (8, 64)	23 (3, 58)	0.749
Patients with age≥18years, n (%)	23 (82.1)	35 (64.8)	0.102	9 (75.0)	49 (70.0)	0.993
Clinical presentation at onset, n (%)						
Epileptic seizures	21 (75.0)	31 (57.4)	0.117	10 (83.3)	42 (60.0)	0.220
Status epilepticus	13 (46.4)	9 (16.7)	0.004	6 (50.0)	16 (22..9)	0.108
Psychiatric symptoms	23 (82.1)	41 (75.9)	0.519	8 (66.7)	56 (80.0)	0.513
Conscious disturbance,	17 (60.7)	26 (48.1)	0.280	7 (58.3)	36 (51.4)	1.000
Memory deficit	15 (53.6)	20 (37.0)	0.151	11 (91.7)	24 (34.3)	<0.001
Severe infection, n (%)	12 (42.9)	9 (16.7)	0.01	8 (66.7)	13 (18.6)	0.002
Ventilatory support, n (%)	7 (25.0)	5 (9.3)	0.113	5(41.7)	7 (10.0)	0.015
mRS score at day one (median, range)	4.5 (3, 5)	3 (1, 5)	<0.001	5 (3, 5)	4 (1, 5)	0.001
mRS score at discharge (median, range)	4 (2, 5)	1 (0, 5)	<0.001	3 (2, 5)	2 (0, 5)	0.02
Length of hospital stay (median, range)	37.5 (10, 111)	25 (5, 54)	<0.001	37.5 (11, 60)	27.5 (5, 111)	0,178
Onset-to-MR time (median, range)	60 (30, 375)	38.5 (2, 1464)	0.034	70 (20, 189)	40.5 (2, 1464)	0.051
Limited response to treatment, n (%)	15 (53.6)	6 (11.1)	<0.001	3 (25.0)	18 (25.7)	1.000
First line combined with second line treatment, n (%)	16 (57.1)	22 (40.7)	0.158	3 (25.0)	35 (50.0)	0.109
CSF abnormalities, n (%)	19 (67.9)	36 (66.7)	0.913	11 (91.7)	44 (62.9)	0.103
Antibody titers (median, range)	1:66 (1:1, 1:320)^{A}	1:32 (1:1, 1:100)^{a}	0.063	1:32 (1:3.2, 1:320)^{B}	1:32 (1:1, 1:320)^{b}	0.979
Vitamin B1 (nmol/L, median, range)	51.3 (44.4, 123.6)^{C}	69.5 (40.0, 143.9)^{c}	0.473	77.5 (41.5, 143.9)^{D}	65.8 (40.0, 141.4)^{d}	0.476
Vitamin B2 (μ g/L, median, range)	198.6 (184.2, 379.5)^{E}	231.7 (178.1, 398.9)^{e}	0.972	195.2 (184.2, 263.2)^{F}	229.5 (178.1, 398.9)^{f}	0.283
Vitamin B6 (μ mol/L, median, range)	21.2 (10.3, 45.9)^{G}	20.9 (7.5, 77.6)^{g}	0.596	17.6 (10.3, 24.0)^{H}	22.1 (7.5, 77.5)^{h}	0.095
Vitamin B12 (pg/mL, median, range)	222.5 (170.5, 487.4)^{I}	256.7 (184.1, 420.7)^{i}	0.127	216.1 (184.2, 311.3)^{J}	256.3 (170.5, 487.4)^{j}	0.1
Folic acid (nmol/L, mean±SD)	10.0± 4.4^{K}	11.8±3.2^{k}	0.34	13.1±5.5^{L}	10.4±3.6^{l}	0.271
25 hydroxyvitamin D3 (nmol/L, median, range)	39.5 (22, 90)^{M}	64.1 (25, 120)^{m}	0.001	63.5 (25, 90)^{O}	55.7 (22, 120)^{o}	0.404

NMDAR, N-methyl-d-aspartate receptor; GCA, global cortical atrophy; MTA, temporal lobe atrophy; F, female; M, male; y, year; mRS, modified Rankin Scale; MR, magnetic resonance; CSF, cerebrospinal fluid; SD, Standard Deviation.

A, N=22; a, N=43; B, N=12; b, N=53; C, N=23; c, N=43; D, N=9; d, N=57; E, N=17; e, N=39; F, N=6; f, N=50; G, N=22; g, N=44; H, N=8; h, N=58; I, N=24; i, N=44; J, N=10; j, N=58; K, N=11; k, N=9; L, N=3; l, N=17; M, N=22; m, N=39; O, N=9; o, N=52.

Table 4 Comparison of encephalatrophy in NMDAR-Ab positive female patients with and without teratomas

	NMDAR-Ab (+) patients with teratomas	NMDAR-Ab (+) patients without teratomas	P
	N=17	N=31	
Mean age (y, mean±SD)	23.2± 5.6	23.0± 10.6	0.503
GCA(+), n (%)	12 (70.6)	9 (29.0)	0.006
MTA (+), n (%)	1 (5.9)	5 (16.1)	0.568
Status epilepticus, n (%)	8 (47.1)	7 (22.6)	0.272
Severe infection, n (%)	9 (52.9)	9 (29.0)	0.102
mRS score at day one (median, range)	5 (3, 5)	4 (2, 5)	0.037
mRS score at discharge (median, range)	3 (0, 5)	2 (0, 5)	0.033
Vitamin B1 (nmol/L, median, range)	80.2 (47.7, 108.0)[A]	69.4 (40.0, 143.9)[a]	0.796
Vitamin B2 (μ g/L, median, range)	196.4 (178.3, 379.5)[B]	256.3 (179.2, 378.4)[b]	0.172
Vitamin B6 (μ mol/L, median, range)	19.9 (12.7, 35.2)[C]	21.6 (10.2, 52.6)[c]	0.926
Vitamin B12 (pg/mL, median, range)	292.4 (190.1, 487.4)[D]	251.0 (170.5, 456.3)[d]	0.08
Folic acid (nmol/L, mean±SD)	5.8±1.2[E]	11.8±3.9[e]	0.024
25 hydroxyvitamin D3 (nmol/L, median, range)	36 (22, 92)[F]	57.6 (23, 120)[f]	0.096

NMDAR-Ab, N-methyl-d-aspartate receptor antibody; y, year; SD, Standard Deviation; GCA, global cortical atrophy; MTA, temporal lobe atrophy; mRS, modified Rankin Scale.

A, N=9; a, N=27; B, N=7; b, N=21; C, N=9; c, N=26; D, N=10; d, N=27; E, N=3; e, N=11; F, N=10; f, N=23.

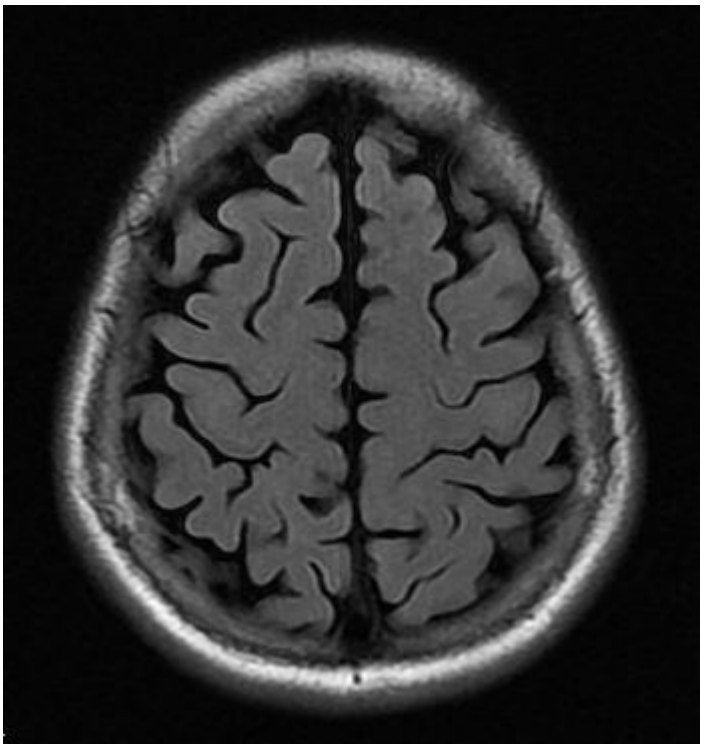


Fig. 1. FLAIR MRI (TR 8400, TE 148.4) showing GCA according to Pasquier and co-workers (mild GCA, score 2)

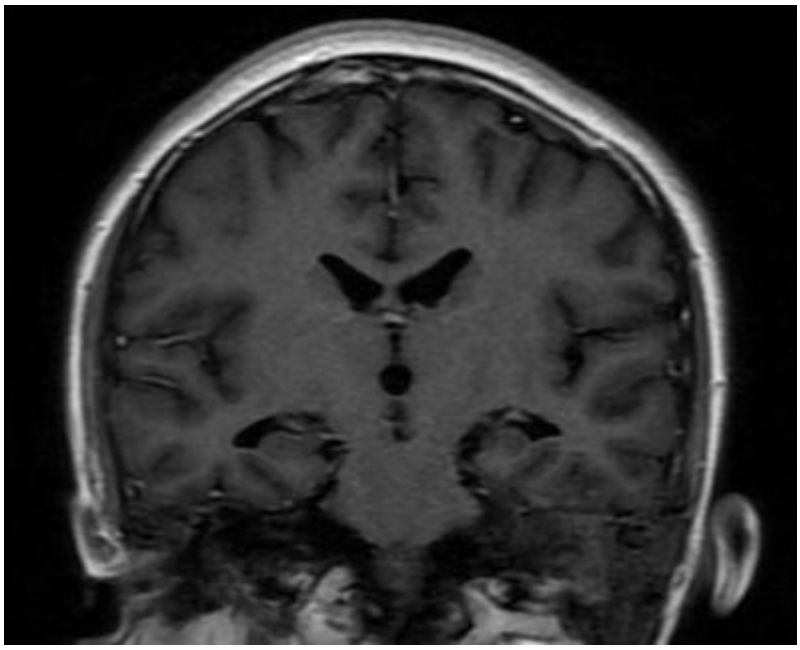


Fig. 2. T1 MRI (TR 1791.4, TE 19.2) showing MTA according to Scheltens and co-workers (score 2).

Figures

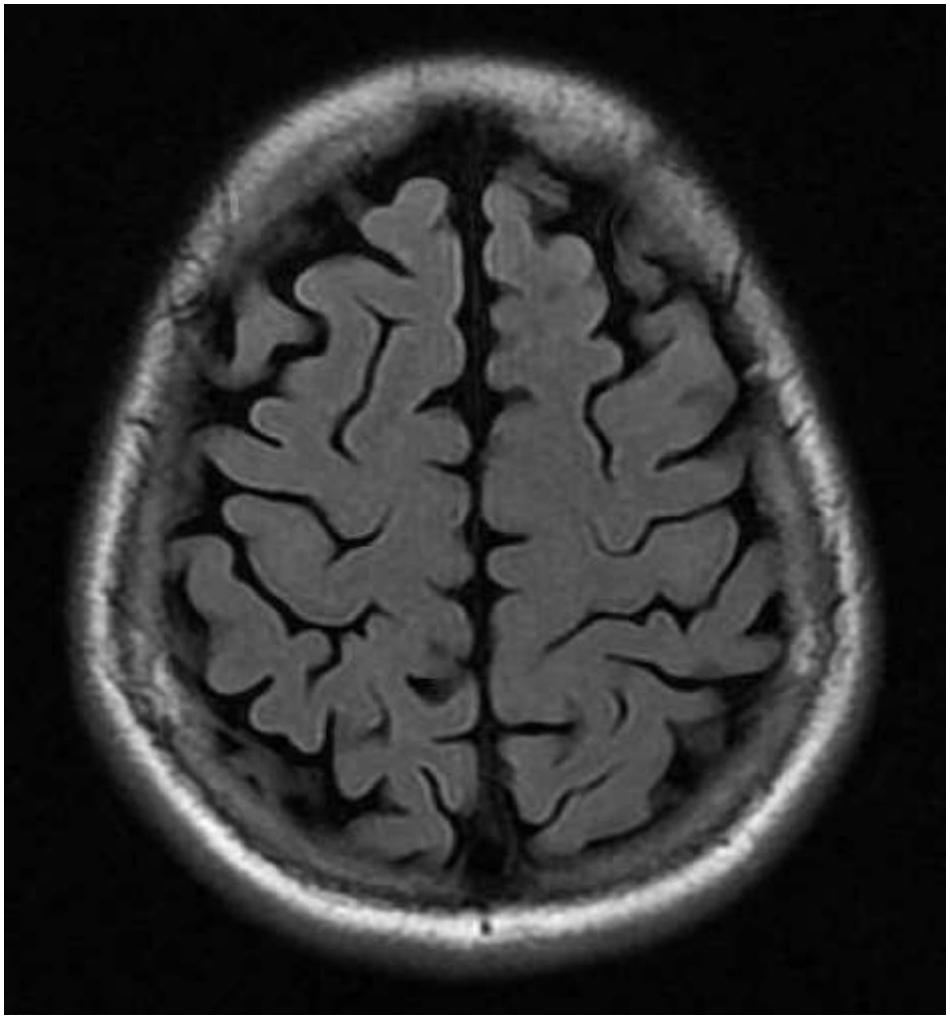


Figure 1

FLAIR MRI (TR 8400, TE 148.4) showing GCA according to Pasquier and co-workers (mild GCA, score 2)

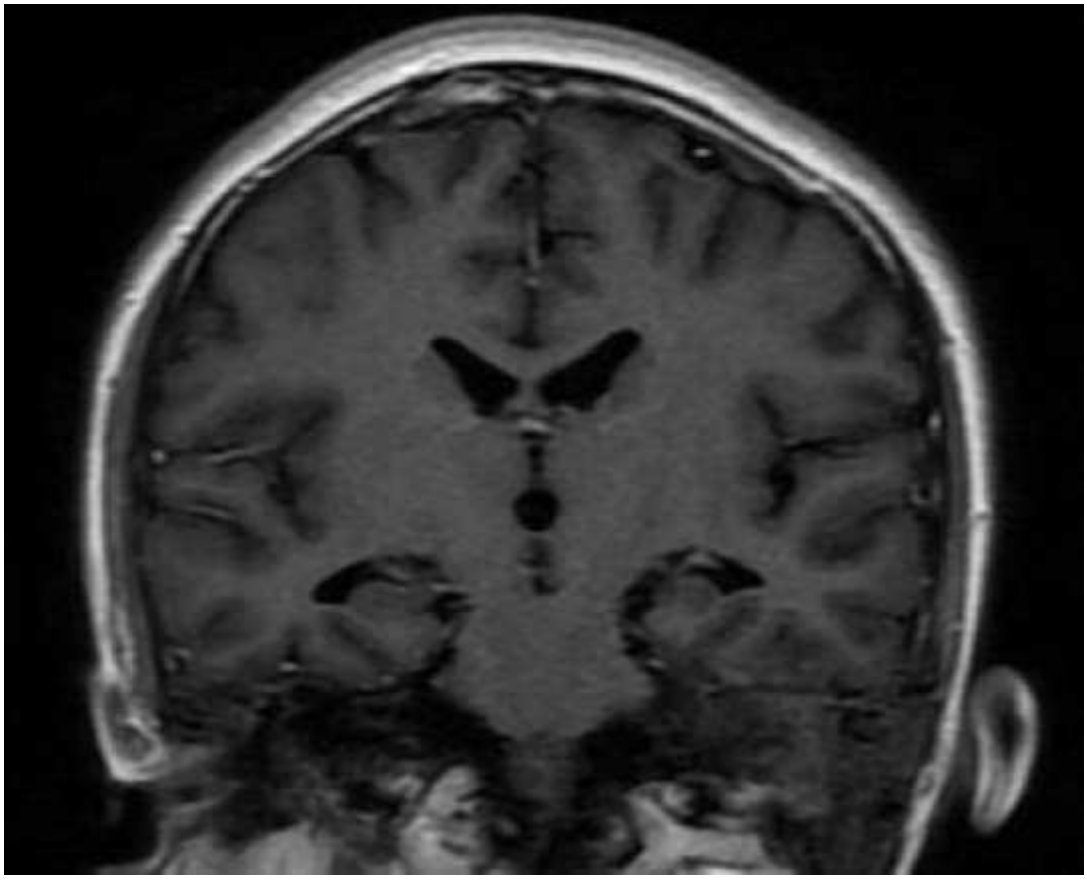


Figure 2

T1 MRI (TR 1791.4, TE 19.2) showing MTA according to Scheltens and co-workers (score 2).