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Original Article

Deficiency of adenosine deaminase 2; special focus on central nervous system imaging

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ABSTRACT

Purpose. – To increase the knowledge of central nervous system (CNS) imaging features in deficiency of adenosine deaminase 2 (DADA2) by examining magnetic resonance imaging (MRI) studies of a relatively large number of patients.
Methods. – We retrospectively examined neuroimages of 12 patients (7 male, 5 female) diagnosed with DADA2. The mean age of the patients at the time of initial brain MRI was 16.7 ± 10.2 years. Seven patients (58.3%) fulfilled the classification criteria of polyarteritis nodosa. Brain MRI studies were assessed with respect to findings of ischemia, intracranial hemorrhages, focal parenchymal signal abnormalities, cerebral/cerebellar volume loss, and abnormal contrast enhancement. Angiographic studies of 7 patients were evaluated for the signs of vasculitis.
Results. – The most frequent finding was acute and/or chronic lacunar ischemic lesions in the brainstem and/or deep gray matter (n = 9, 75%). Six patients (50%) revealed MRI findings compatible with recurrent ischemic attacks. Small nodular contrast enhancement (n = 2, 16.6%), acute putaminal hemorrhage (n = 1, 8.3%) and findings compatible with posterior reversible encephalopathy syndrome (n = 1, 8.3%) were also detected. Slight-to-moderate diffuse cerebral and/or cerebellar volume loss (n = 7, 58.3%), decreased T1 signal of the bone marrow (n = 6, 50%) and optic atrophy (n = 1, 8.3%) were the other findings on brain MRI. The only abnormal angiographic finding was reduced caliber of the right distal posterior cerebral artery in MRA of a patient (14.6%).
Conclusion. – DADA2 should be included in the differential diagnosis of young patients presenting with ischemic and/or hemorrhagic lesions located in the brainstem and deep gray matter, especially if they have a family history or additional systemic abnormalities.

Introduction

Deficiency of adenosine deaminase 2 (DADA2) is a recently defined auto-inflammatory disorder characterized by mild immunodeficiency and features of early onset polyarteritis nodosa (PAN)-like vasculopathy [1,2]. DADA2 arises secondary to loss-of-function mutations in cat eye syndrome chromosome region candidate 1 (CECR1) gene that encodes adenosine deaminase 2 (ADA2) [1–4].

ADA2 plays an important role in immune regulation through its effects on extracellular adenosine and leukocyte development as well as macrophage differentiation [2,3]. It has also been suggested to act as a growth factor for endothelial cells and to maintain vascular integrity [2,3,5]. Both decreased levels and lower enzymatic activity of ADA2 are associated with various manifestations related to involvement of the skin, kidneys, gastrointestinal tract and the nervous system in DADA2 patients [2–7]. The clinical picture is indistinguishable from PAN in most cases and varies widely in terms of severity [1,3,4,6,7]. Most common manifestations include intermittent fever, arthralgia, livedo racemosa, early onset stroke and peripheral neuropathy [2–7].

The knowledge of central nervous system (CNS) imaging findings in DADA2 comes from a few case reports and case series. The major brain magnetic resonance imaging (MRI) findings described

Abbreviations: ADA2, adenosine deaminase 2; CECR1, chromosome region candidate 1; DADA2, deficiency of adenosine deaminase 2; PAN, polyarteritis nodosa; PRES, posterior reversible leukoencephalopathy syndrome; TNF, tumor necrosis factor.

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so far are lacunar infarctions/hemorrhages located in the brainstem and deep brain nuclei [2,5,6,8–11]. Cerebral angiographic imaging of few cases in literature has revealed no apparent findings suggestive of vasculitis [2,5].

Familiarity with CNS imaging findings of this recently recognized entity facilitates timely diagnosis and treatment with anti-TNF agents which were confirmed to effectively control inflammatory manifestations and occurrence of vascular events [6,7]. Therefore, the present study aims to increase the knowledge of CNS imaging findings in DADA2 through describing imaging patterns and revealing previously undefined findings in a relatively large group of patients.

Methods

Patients

We retrospectively evaluated neuroimaging studies of 12 patients (7 male, 5 female) who were diagnosed with DADA2 at Hacettepe University Pediatric and Adult Rheumatology Departments between 2014 and 2016. DADA2 diagnosis was genetically confirmed in all patients. Patient demographics, clinical features, laboratory and histopathologic findings, treatment schemes were acquired from patient charts available in the hospital information system. The local institutional ethics board approved this retrospective study.

Neuroimages

We evaluated a total of 18 brain and 3 spinal MRIs scanned between November 2007 and February 2016. All patients had at least one brain MRI; 5 patients (41.6%) had follow-up studies. Only the technically adequate brain MRIs with diffusion-weighted images were included in the study. Therefore, a follow-up study of one patient with lost images due to archiving defect was excluded. MRIs were performed at 1.5 T scanners (Symphony, Siemens, Erlangen, Germany or Achieva, Philips Healthcare, Best, Netherlands). Routine brain MRI protocol with sagittal and axial T1 W (TR/TE; 550–650/15–20 ms), coronal and axial T2 W (TR/TE; 2800–3800/100–120 ms), axial FLAIR (TR/TE/TI; 8000–8500/100–120/2000–2100 ms) and DWI (Echo planar imaging applied at 3-b values with a maximum of 1000 s/mm^2; TR/TE of 4500–5100/137–145 ms) sequences was performed in all studies. The images with a 5-mm-slice thickness and no interslice gap were obtained from all imaging sequences. Seven brain MRIs including one follow-up study had additional post-contrast axial and coronal T1 W images.

All spinal MRIs had a routine protocol including sagittal and axial T1 W and T2 W sequences (TR/TE; 400-–600/7–12 ms, TR/TE; 5200–3100/80–120 ms, respectively) with a 3-mm-slice thickness.

We also assessed 9 cerebral TOF 3D Multislab MRA studies added to initial ($n = 6$) and follow-up ($n = 3$) brain MRIs of six patients, two cerebral DSA studies performed for confirmation of MRA findings of two patients and a cerebral CTA study.

Image evaluation

All studies were evaluated in consensus by two neuroradiologists with an experience of 17 (KKO) years and 3 years (EB). Based upon imaging findings obtained from the previous reports in the literature, all brain MRIs were assessed in terms of the presence, location and size of acute or chronic ischemic lesions/lacunar infarctions and intracranial hemorrhages. We also noted concomitant abnormal findings including cerebral/cerebellar volume loss, focal parenchymal T2 hyperintense abnormalities and decreased T1 signal intensity of bone marrow. The presence and the pattern of abnormal contrast enhancement were evaluated on brain MRIs when post-contrast images were available.

We evaluated angiographic studies in terms of typical signs of vasculitis, such as “beads on string” appearance, focal narrowing, occlusions, dilation and aneurysms in the cerebral vessels.

Spinal MRIs were studied in terms of cord atrophy and the presence, location and extent of abnormal signal intensity.

Statistical analysis

Descriptive statistics were demonstrated as mean ± standard deviation or median (minimum–maximum) for quantitative variables and categorical variables were summarized as the number of cases and (%).

Results

Clinical assessment

Patient demographics, clinical and laboratory features were summarized in Table 1. Genetic analysis was performed by Sanger sequencing of CECR1 in all patients. The majority of patients ($n = 9$, 75%) had their first symptoms under the age of 18 years. Seven patients (58.3%) had been followed up with the diagnosis of systemic PAN, fulfilling the Ankara 2008 classification criteria [12]. Histopathology of skin biopsies revealed vasculitis of small and/or middle sized vessels compatible with PAN in four patients (33.3%). Abdominal CTA detected microaneurysms involving bilateral segmental branches of the renal arteries and/or intraparenchymal branches of the hepatic arteries in 3 patients (25%).

Two adult patients died soon after the diagnosis of DADA2 following pulmonary hemorrhage and necrotizing pneumonia, respectively. One patient was asymptomatic on colchicine treatment for almost 10 years. Rest of the patients responded well to anti-tumor necrosis factor therapy (etanercept^R) and did not show any neurological symptoms after treatment.

Neuroimaging findings

The mean age of the patients at the time of first brain MRI was 16.7 ± 10.2 years of age. MRI findings and related clinical symptoms were summarized in Table 2. Briefly, four patients (33.3%) showed acute ischemic lesions located in the midbrain, pons and medulla. Of these, three patients were under 7 years old; median age was 5.5 (2–41) years. All ischemic lesions were smaller than 7 mm in diameter. One patient (no. 12) presented with two recurrent ischemic attacks in a 6 months period and MRIs revealed acute left lateral medullary and right lateral ponto-mesencephalic junction infarctions, respectively (Fig. 1a–b). There was no hemorrhagic signal change accompanying the acute ischemic lesions. On the other hand, a large acute parenchymal hematoma was detected in the left putamen of a patient (no. 5) presenting with stroke (Fig. 1c).

MRI revealed chronic ischemic lesions in the basal ganglia, thalami and pons in 7 patients (58.3%) with or without acute ischemia (Fig. 1d). A few punctate T2 hyperintense periventricular and peripheral white matter lesions detected in 3 of these patients were also suggestive of small vessel ischemia. Totally, acute and/or chronic ischemic lesions were observed in 9 (75%) of the patients. Six of them revealed MRI findings compatible with recurrent ischemic attacks.

Small (< 5 mm) nodular/punctate parenchymal contrast enhancement was detected in 2 (33.3%) of the patients having Gd-enhanced T1W images. Punctate area of restricted diffusion located in the left posteromedian mesencephalon in one patient (no. 8) demonstrated contrast enhancement. MRI of another

Table 1
The characteristics of adult and pediatric patients with deficiency of adenosine deaminase 2 (DADA2).

	Total patients	Adult patients	Pediatric patients
General features			
Number of patients (%)	12 (100)	6 (50)	6 (50)
Age of onset, median (min–max)	5.25 (1.5–35) years	8.5 (2–35) years	3.75 (1.5–14) years
Age at diagnosis, median (min–max)	17.25 (3–45) years	21.5 (17–45) years	11.3 (3–17.5) years
Gender, male *n* (%)/female *n* (%)	7 (58.3)/5 (31.7)	4 (66.6)/2 (33.4)	3 (50)/3 (50)
Consanguinity *n* (%)	6 (50)	2 (33.3)	4 (66.6)
CECR1 gene mutation, *n* (%)	9 (75)→G47R/G47R 2 (16.7)→G47R/– 1 (8.4)→G47R/G47V	4 (66.7)→G47R/G47R 1 (16.7)→G47R/– 1 (16.7)→G47R/G47V	5 (83.3)→G47R/G47R 1 (16.7)→G47R/–
Fulfilling the PAN criteria, *n* (%)	7 (58.3)	5 (83.3)	2 (33.3)
Clinical features			
Fever, *n* (%)	12 (100)	6 (100)	6 (100)
Recurrent abdominal pain, *n* (%)	12 (100)	6 (100)	6 (100)
Myalgia, *n* (%)	12 (100)	6 (100)	6 (100)
Arthralgia, *n* (%)	11 (91.6)	6 (100)	5 (83.3)
Weakness, *n* (%)	11 (91.6)	5 (82.3)	6 (100)
Livedo reticularis, *n* (%)	11 (91.6)	5 (83.3)	6 (100)
Fatigue, *n* (%)	9 (75)	5 (83.3)	4 (66.6)
Arthritis, *n* (%)	9 (75)	5 (83.3)	4 (66.6)
Stroke, *n* (%)	7 (58.3)	4 (66.6)	3 (50)
Peripheral neuropathy, *n* (%)	7 (58.3)	2 (33.3)	4 (66.6)
Panniculitis/Erythema nodosum, *n* (%)	6 (50)	3 (50)	3 (50)
Hepatosplenomegaly, *n* (%)	5 (41.6)	3 (50)	2 (33)
Diarrhea, *n* (%)	5 (41.6)	3 (50)	1 (16.7)
Weight loss, *n* (%)	4 (33.3)	3 (50)	1 (16.7)
Raynaud's phenomenon, *n* (%)	4 (33.3)	3 (50)	1 (16.7)
Testicular involvement, *n* (%)	3 (23.1)	2 (33.3)	1 (16.7)
Night sweats, *n* (%)	3 (25)	3 (50)	0 (0)
Flank pain, *n* (%)	2 (16.7)	1 (16.7)	1 (16.7)
Vomiting, *n* (%)	1 (8.3)	0 (0)	1 (16.7)
Seizures, *n* (%)	1 (8.3)	1 (16.7)	0 (0)
Pancreatitis, *n* (%)	1 (8.3)	1 (16.7)	0 (0)
Spinal cord involvement, *n* (%)	1 (8.3)	0 (0)	1 (16.7)
Optic neuritis, *n* (%)	1 (8.3)	1 (16.7)	0 (0)
Digital ulcers, *n* (%)	1 (8.3)	1 (16.7)	0 (0)
Comorbidity			
Hypertension, *n* (%)	4 (33.3)	3 (50)	1 (16.7)
Amyloidosis, *n* (%)	1 (8.3)	1 (16.7)	0 (0)
Diabetes mellitus, *n* (%)	1 (8.3)	1 (16.7)	0 (0)
Hemophagocytic syndrome, *n* (%)	1 (8.3)	0 (0)	1 (16.7)
Laboratory findings			
Proteinuria (> 150 mg/day), *n* (%)	7 (58.3)	6 (100)	1 (16.7)
Low IgM level, *n* (%)	3 (25)	2 (33.3)	1 (16.7)
Lymphopenia, *n* (%)	3 (25)	3 (50)	0 (0)
Hypercoagulopathy, *n* (%)	1 (8.3)	1 (16.7)	0 (0)

patient (no. 3) revealed milimetric nodular contrast enhancements with no associated restricted diffusion in the right caudate nucleus and putamen (Fig. 1e–f).

MRI findings compatible with posterior reversible leukoencephalopathy syndrome (PRES) were detected in a patient (no. 11) who presented with hypertension and the diagnosis of mesangial proliferative glomerulonephritis (Fig. 1g–h). The diagnosis of PRES was also confirmed with clinical improvement after control of hypertension.

In 7 patients with cerebral angiography studies (58.3%), we detected MRA abnormality in only one patient (14.2%); decreased caliber of the right distal posterior cerebral artery (no. 8). Neither cerebral CTA nor DSA were performed to confirm the detected MRA finding.

Slight-to-moderate diffuse cerebral and/or cerebellar volume loss ($n = 7$; 58.3%), decreased T1 signal of the bone marrow ($n = 6$; 50%), optic atrophy ($n = 1$; 8%) were other accompanying MRI findings in the present series.

Spinal MRI revealed atrophy and diffuse central T2 hyperintensity in the spinal cord in a 14-year-old patient (no. 6) who presented with sensorimotor axonal type of polyneuropathy.

Discussion

DADA2 has been recently recognized and not extensively studied in contrast to ADA1 deficiency, which is associated with severe combined immunodeficiency. Previous reports on DADA2 have concentrated on the genetic basis, pathophysiology and clinical manifestations of the disease; and the studies particularly focusing on CNS imaging are lacking in the literature. CNS involvement is one of the main features of DADA2 and could be disabling, therefore understanding its pattern could be very useful in the management of the disease.

In this retrospective study, we present the CNS features of the disease from a radiologic point of view. This represents the largest group of DADA2 patients with detailed CNS imaging evaluation to date.

DADA2 presents with a wide spectrum of clinical manifestations ranging from systemic inflammation to cutaneous or visceral PAN like vasculopathy and early onset stroke [1–6]. Neurological manifestations reported so far include TIA, ischemic or hemorrhagic stroke and peripheral neuropathy [1–6,8,9]. Early onset of the symptoms [median: 5.2 (1.5–35) years] in our patient group reflects the genetic basis of the disease. The clinical manifestations were

Table 2
Brain MRI findings and associated neurological features in DADA2 patients.

Patient no./sex	MRI no./age at MRI (years)	Clinical presentation/MRI indication	Brain MRI findings		
			Ischemic/hemorrhagic lesion (location)	Other	Pathologic enhancement (location/pattern)
1/F	1/2	Strabismus, restriction of inward gaze in R eye, ataxic gait at L side	Acute ischemic (R PM Mes)	–	–
2/F	1/15	Peripheral neuropathy, minimal atrophy in the distal extremity	–	↓ bone marrow T1 signal	N/A
3/M	1/20	Strabismus	Chronic ischemic (head of R CN)	Atrophy and T2 hyperintense signal change in R striatum Minimal cerebral volume loss ↓ bone marrow T1 signal	+ (R striatum/milimetric nodular)
	2/20	3-month follow up	No change	Late subacute hemorrhagic signal change in R striatum	–
4/M	1/22	Visual loss, unilateral hearing loss	Chronic ischemic (R LN)	Few non-specific punctate T2 hyperintense WM lesions R optic atrophy ↓ bone marrow T1 signal	–
5/F	1/20	Vertigo	Chronic ischemic (head of R CN)	–	N/A
	2/21	R hemiparesis, dysarthria	Acute hematoma (L LN)	–	N/A
	3/22	L-sided numbness	–	Few non-specific punctate T2 hyperintense WM lesions	N/A
6/M	1/14	Gait disturbance	Chronic ischemic (R LN)	Minimal cerebral volume loss	N/A
7/F	1/22	Weakness in L hand	–	Minimal cerebral/cerebellar volume loss ↓ bone marrow T1 signal	N/A
8/M	1/41	Diplopia, speech disorder, gait disturbance	Both acute (L PM Mes) and chronic (pons) ischemic	Few non-specific punctate T2 hyperintense WM lesions ↓ bone marrow T1 signal	+ (Ischemic lesion in L PM Mes/punctate)
	2/45	Follow up	↑ In no. of pontine chronic ischemic	+Minimal cerebral/cerebellar volume loss	N/A
9/F	1/4	Diplopia, peripheral neuropathy	Acute ischemic (L lateral pons)	–	N/A
10/M	1/17	Diplopia, nystagmus, dysarthria, L lower extremity weakness, peripheral neuropathy	Chronic ischemic (pons, deep gray nuclei)	Minimal cerebellar volume loss	–
11/M	1/17	L-sided increased DTR, sensory loss at L lower extremity	–	Bilateral temporo-occipital, P-mesial parietal, R frontal cortical and subcortical T2 hyperintense signal changes (PRES) Minimal cerebral-cerebellar volume loss	N/A
12/M	1/7	Lateral medullary syndrome	Acute ischemic (PL medulla)	Minimal cerebral-cerebellar volume loss ↓ bone marrow T1 signal	N/A
	2/8	6th nerve palsy	Acute ischemic (R Ponto-Mes Junction)	No change	N/A

CN: caudate nucleus; L: left; LN: lentiform nucleus; Mes: mesencephalon; N/A: not available; PL: posterolateral; PM: posteromedian; PRES: posterior reversible encephalopathy syndrome; R: right; WM: white matter.

similar to those mentioned in previous studies in terms of the organ systems involved. The most frequent manifestations were systemic inflammatory symptoms including fever and abdominal pain with elevated acute phase reactants (100%), and skin involvement in the form of livedo reticularis (91.6%). All patients demonstrated at least one neurological manifestation either in the form of stroke or peripheral neuropathy.

The majority of our patients ($n = 7$, 58.3%) were followed up with the diagnosis of PAN until DADA2 was described and the genetic confirmation was available. The patients were fulfilling the Ankara 2008 classification criteria; four patients had histopathologic findings, whereas three patients had abdominal CTA findings compatible with PAN. This finding was also similar to previous reports underlying the association of DADA2 with early onset PAN [1,3,4,6]. In children with PAN, neurologic involvement has been reported to occur less frequently compared to skin, musculoskeletal system, renal or GIS involvements [13,14]. Also CECR1 mutation negative PAN patients have been detected to have a later disease onset and a less frequent central nervous system involvement [6]. Therefore, the genetic analysis for DADA2 is highly suggested in early onset PAN patients with positive family history, consanguineous marriage and/or early onset stroke.

The previously described brain MRI findings of DADA2 were compatible with small sized vasculopathy and involved lacunar infarctions/hemorrhages located in the brainstem and deep brain nuclei [2,5,8–11]. We detected acute and/or chronic ischemic lesions in brain MRIs of 9 patients (75%); six of them had findings of recurrent ischemic episodes. All of the acute lacunar infarctions were located in the brainstem; the chronic ischemic lesions additionally involved deep brain nuclei. A punctate mesencephalic restricted diffusion demonstrated Gd enhancement in a patient. Another patient showed a few small nodular contrast enhancement superimposed on chronic-atrophic changes in the right basal ganglion without an associated restricted diffusion. These two findings could be attributed to contrast enhancement of small subacute ischemic lesions or an active inflammatory-vasculitic process.

Intracerebral hemorrhage has not been reported as frequent as cerebral ischemia in previous reports with frequencies varying

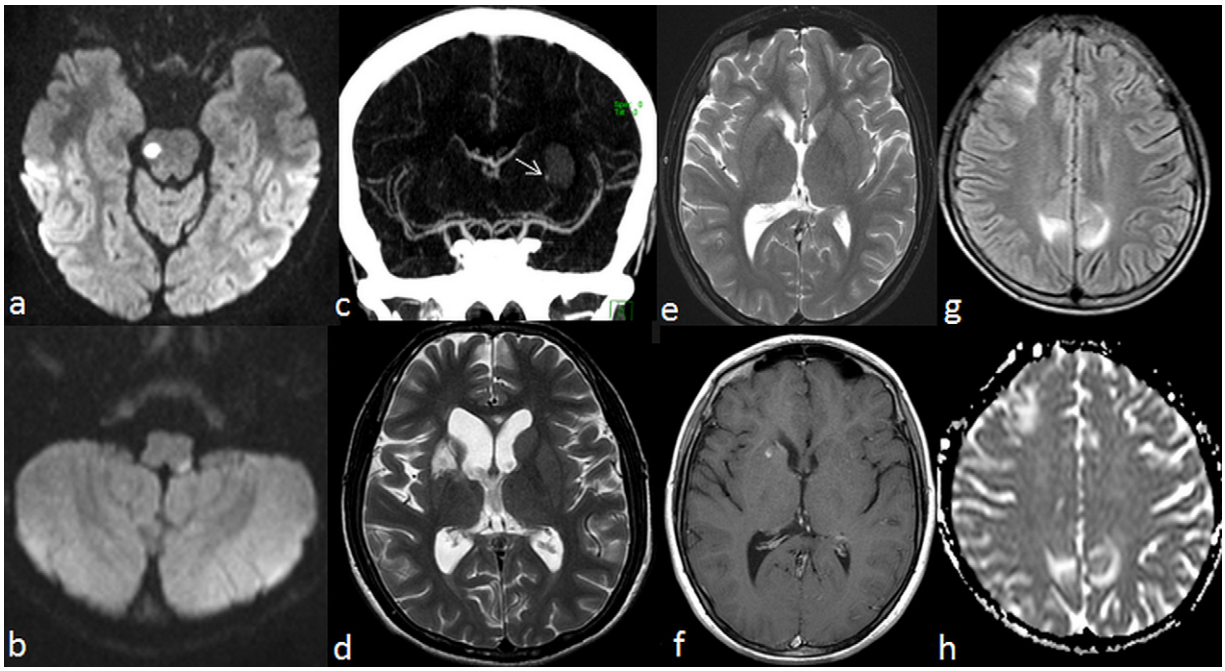

Fig. 1. Brain MRI findings in DADA2 patients. The DWIs performed at the time of recurrent ischemic attacks show acute ischemic lesions located at the right lateral pontomesencephalic junction (a) and the left lateral medulla oblongata (b) in a patient (no. 12). The coronal reformatted CTA (c) of a patient (no. 5) demonstrates an acute hematoma in the left basal ganglion with a "spot sign" suggestive of active bleeding (arrow). Axial T2W image (d) shows chronic lacunar infarction and resulting volume loss in the right basal ganglion in a patient (no. 4). Axial T2W (e) and Post-Gd (f) images show abnormal milimetric contrast enhancement superimposed on previous changes in the right basal ganglion of a patient (no. 3). Axial FLAIR image (g) and ADC map (h) show subcortical hyperintense signal changes in bilateral posterior parietal and right frontal watershed areas compatible with PRES in a patient (no. 11).

between 4–33%. It was also an uncommon finding in our study; one patient showed an acute hematoma located in the basal ganglion. The parenchymal hemorrhage could be secondary to vasculopathic changes or hypertension that accompanied the clinical picture in this case.

Beside ischemic or hemorrhagic changes, we also detected previously undefined CNS imaging findings of DADA2. A patient with renal disease and hypertension revealed findings compatible with PRES. We also observed atrophy and long central T2 hyperintensity in the spinal cord of a patient. This may represent the inflammatory involvement of the spinal cord. However, this finding has not been reported previously and needs further observations to unravel its pathophysiological origin.

Slight-to-moderate diffuse cerebral and/or cerebellar volume loss and decreased T1 signal of the bone marrow were the other relatively common findings in our study. These findings could be explained respectively by chronic-vasculopathic nature of the disease and increased hematopoietic activity to compensate anemia seen in some of the patients with DADA2.

The knowledge about CNS angiographic findings in DADA2 patients is limited and stems from a few cases in literature [2,5,8]. Garg et al. reported findings of irregular narrowing in the right middle cerebral artery in a 5-year-old patient with cerebral hemorrhage, although this finding could also be attributed to possible vasospasm following intracranial hemorrhage [8]. Zhou et al. reported normal angiogram findings in five patients with stroke, all having MRA and three of them having additional DSA [2]. They also revealed brain biopsy findings of two patients which involved extravasation of erythrocytes around small vessels without a significant inflammation. These histopathologic findings along with the absence of any remarkable angiographic features compatible with vasculitis have suggested that other pathophysiological mechanisms, such as vasospasm or interruption of endothelial integrity, may contribute to the CNS features. On the other hand, it is apparently known that angiographic images including cerebral DSA could be normal in small vessel CNS vasculitis and there is not enough data from few existing brain biopsies to accept such presumption. Our study revealed abnormal MRA findings in only one patient; thinning of the distal posterior cerebral artery. The cerebral angiographic findings which are highly suggestive of vasculitis such as "beads on a string", occlusions or aneurysms were not detected, although some patients ($n = 3$) had aneurysms typical for PAN in mid-sized abdominal arteries. This observation could suggest that different mechanisms may be operative in vascular involvement of CNS and other organ systems.

Our study has some limitations due to its retrospective design. Firstly, not all of the patients had angiographic or post-Gd studies; therefore evaluations of cerebral vasculature and contrast enhancement were limited to eight and seven patients, respectively. Secondly, angiographic evaluation was performed by MRA in most patients and the abnormal findings were not confirmed by DSA. Additionally, image evaluation was suboptimal in terms of microhemorrhage detection, because SWI was not included in our routine brain MRI protocol. These limitations could be overcome by a prospective study designed with dedicated MRI protocols and appropriate angiographic study scheme.

Conclusion

CNS involvement is very frequent in DADA2 patients. Increased awareness for DADA2 among radiologists is important since effective treatment is different (anti-TNF) than other causes of stroke. Therefore, DADA2 should especially be in the differential in young patients with ischemic and hemorrhagic lesions located in the brainstem and the basal ganglia who have a family history or additional systemic abnormalities such as recurrent fever, abdominal pain, and skin lesions.

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Ethical statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

For this type of study formal consent is not required.

Disclosure of interest

The authors declare that they have no competing interest.

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