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ORIGINAL ARTICLE

Neurological phenotype of adenosine deaminase 2 deficient patients: a cohort study

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Abstract

Background and purpose: Patients with adenosine deaminase 2 (ADA2) deficiency can present with various neurological manifestations due to vasculopathies and autoinflammation. These include ischaemic and hemorrhagic stroke, but less clearly defined neurological symptoms have also been reported.

Methods: In this cohort study, patients with confirmed ADA2 deficiency from seven university hospitals in the Netherlands were included. The frequency and recurrence rates of neurological manifestations before and after initiation of tumor necrosis factor α (TNF-α) inhibiting therapy were analyzed.

Results: Twenty-nine patients were included with a median age at presentation of 5 years (interquartile range 1–17). Neurological manifestations occurred in 19/29 (66%) patients and were the presenting symptom in 9/29 (31%) patients. Transient ischaemic attack

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(TIA)/ischaemic stroke occurred in 12/29 (41%) patients and was the presenting symptom in 8/29 (28%) patients. In total, 25 TIAs/ischaemic strokes occurred in 12 patients, one after initiation of TNF-α inhibiting therapy and one whilst switching between TNF-α inhibitors. None was large-vessel occlusion stroke. Two hemorrhagic strokes occurred: one aneurysmatic subarachnoid hemorrhage and one spontaneous intracerebral hemorrhage. Most neurological symptoms, including cranial nerve deficits, vertigo, ataxia and seizures, were caused by TIAs/ischaemic strokes and seldom recurred after initiation of TNF-α inhibiting therapy.

Conclusions: Neurological manifestations, especially TIA/ischaemic stroke, are common in patients with ADA2 deficiency and frequently are the presenting symptom. Because it is a treatable cause of young stroke, for which antiplatelet and anticoagulant therapy are considered contraindicated, awareness amongst neurologists and pediatricians is important. Screening for ADA2 deficiency in young patients with small-vessel ischaemic stroke without an identified cause should be considered.

KEYWORDS
ADA2 deficiency, pediatric stroke, young stroke

BACKGROUND

Adenosine deaminase 2 (ADA2) deficiency is an autosomal recessive disorder caused by loss of function variants in the *ADA2* gene (formerly *CECR1*). It was first described in 2014 as a monogenic systemic vasculitis syndrome [1, 2], but it has since come to light that patients with ADA2 deficiency may present with a spectrum of symptoms varying in severity, including manifestations of immunodeficiency, autoinflammation, hematological abnormalities and vasculopathies [3, 4]. A previous study by Jee et al. [5] estimated a carrier frequency of at least 1 in 236 individuals, which would correspond to over 30,000 cases of ADA2 deficiency worldwide. Less than 500 cases have been identified thus far, demonstrating that the disease remains highly underrecognized.

The exact function of ADA2 and the underlying mechanism by which decreased ADA2 enzyme activity leads to different disease manifestations is not entirely known. It is known that ADA2 is primarily expressed in monocytes and macrophages, and in vitro studies have shown that ADA2 deficient monocytes are polarized towards the proinflammatory M1 subtype [1, 6]. Proinflammatory M1 monocytes and macrophages are thought to be the source of production of tumor necrosis factor (TNF) cytokine, which probably plays an important role in the development of vasculopathies in these patients [7]. As such, TNF-α inhibitors are currently the mainstay therapy for these patients.

From the outset, it has been recognized that ischaemic stroke is a predominant feature in patients with ADA2 deficiency [1, 2, 8]. Since then, several other neurological manifestations have been described, including hemorrhagic stroke and peripheral neuropathy [9–11]. Some less clearly defined neurological symptoms and disorders have also been reported, such as recurrent headaches, episodic vertigo, ataxia, cranial nerve deficits and seizures [9, 10, 12–15]. For most of these neurological symptoms and disorders, little is known about underlying pathophysiology and frequency of occurrence. Although it has previously been shown that the recurrence risk of ischaemic stroke during TNF-α inhibiting therapy is very low [4], the likelihood of recurrence of other neurological manifestations is unknown.

In this study, the characterization, incidence and recurrence rates of stroke and other neurological manifestations are analyzed in a cohort of Dutch patients with ADA2 deficiency. Furthermore, the importance of ADA2 deficiency awareness in neurological practice is discussed, especially the usefulness of screening for ADA2 deficiency in young stroke patients and the risks of treatment with antiplatelet and anticoagulant therapy in ADA2 deficient patients.

METHODS

Study design and population

Patients were identified by contacting all physicians of the immunology departments of all seven university hospitals in the Netherlands and by searching the Eurofever Registry and the Dutch National Immunodeficiency Database. The Eurofever Registry is an ongoing, prospective, European registry of patients with autoinflammatory diseases initiated by the Paediatric Rheumatology International Trials Organization [16]. The Dutch National Immunodeficiency Database is an ongoing prospective study on immunodeficiencies in the Netherlands. In the current study, all patients with confirmed ADA2 deficiency based on homozygous or compound heterozygous loss of function variant in *ADA2* who were identified from 2014 until March 2022 were included. This cohort was previously published by Andriessen et al. [17]. Clinical data on neurological symptoms and disorders, laboratory and genetic tests, imaging studies, treatment and clinical course were recorded using a standardized case record

form (Appendix). Missing data were collected retrospectively by the patients' treating physicians through chart review.

Permission to carry out the Eurofever Registry in the Netherlands and approval for the Dutch National Immunodeficiency Database were granted by the medical ethics committee of the Erasmus University Medical Center in Rotterdam. Informed consent for enrollment was obtained from all patients and/or legal representatives by the treating physician. This study conforms with the World Medical Association Declaration of Helsinki.

Definitions and outcomes

Based on previous literature and the clinical experience of the authors, predefined neurological manifestations of interest were as follows.

(i) Neurological symptoms: headache, vertigo, ataxia, hearing loss, visual loss, cognitive/behavioral disorders, cranial nerve deficits (including optic neuritis) and seizures.
(ii) Neurological disorders: transient ischaemic attack (TIA)/ischaemic stroke, hemorrhagic stroke, central nervous system vasculitis and peripheral neuropathy.

Neurological symptoms were reported by the treating physician based on medical history and neurological examination. Neurological disorders were diagnosed by a board certified (pediatric) neurologist, (pediatric) rheumatologist or pediatrician.

Adenosine deaminase 2 enzyme activity was measured as previously described by Van Montfrans et al. [12] and standard diagnostic assays were used to measure levels of antiphospholipid (aPL) antibodies.

Statistical analysis

Baseline characteristics were reported for the population as a whole and compared between patients with and without any neurological manifestations. The Mann–Whitney *U* test was used for non-normally distributed continuous variables and the chi-squared test for categorical variables. The incidence and recurrence rates before and after initiation of TNF-α inhibiting therapy were calculated for all neurological manifestations of interest. All analyses were performed using SPSS software (version 26; SPSS Inc.).

RESULTS

Twenty-nine patients from seven university hospitals in the Netherlands were included. General patient characteristics for all patients are reported in Table 1. Median age at presentation was 5 years (interquartile range [IQR] 1–17), median age at diagnosis was 20 years (IQR 11–46) and 59% of patients were male. There were five sibling pairs in the cohort. Median ADA2 enzyme activity prior to initiation of TNF-α inhibiting therapy was 0.3 U/L (IQR 0.1–1.0). Patients were followed up for a median of 5 years after diagnosis (IQR 2–8); 17% of patients died during follow-up. As published previously, the most common non-neurological findings in our cohort were cutaneous involvement (e.g., livedo reticularis/racemosa and erythema nodosum, 79%), (hepato) splenomegaly (71%) and recurrent infections (59%). Mortality rate during follow-up was 5/29 (17%). Three patients died of hemophagocytic lymphohistiocytosis (HLH) or HLH-associated complications, one due to a pulmonary malignancy and of bone marrow failure. For detailed information on cause of death, see Andriessen et al. [17].

Neurological manifestations occurred in 19/29 (66%) of included patients. On comparing patients with and without any neurological manifestations, no statistically significant differences were found in general patient characteristics. ADA2 enzyme activity prior to initiation of treatment also did not differ between groups (0.3 vs. 0.3 U/L, $p = 0.66$). Of all included patients, 9/29 (31%) presented with a neurological symptom or disorder. TIA or ischaemic stroke was the presenting manifestation in 8/29 (28%) patients. One of these patients was an untreated, previously asymptomatic, 5-year-old girl who was diagnosed after her older brother was diagnosed with ADA2 deficiency. Ten months later she suffered from medullary infarction as her first ADA2 deficiency related manifestation. One patient (1/29, 3%) presented with cranial nerve deficits, which were attributed to a varicella zoster virus (VZV) infection. The VZV infection was diagnosed based on history and clinical course but could not be confirmed by microbiological testing in blood or spinal fluid or by VZV-associated abnormalities on magnetic resonance imaging (MRI).

The incidence and recurrence rate of neurological manifestations in our cohort are reported in Table 2. The most common neurological manifestations were TIA/ischaemic stroke (12/29; 41%), headache (11/29; 38%) and cranial nerve deficit (11/29; 38%). Most neurological symptoms, including cranial nerve deficits, vertigo and ataxia, were caused by TIAs/ischaemic strokes. Only one patient had a seizure, which was an acute symptomatic seizure caused by ischaemic stroke. No cases of central nervous system vasculitis or peripheral neuropathy were reported in our cohort. Symptoms with the highest recurrence rate were headache (4/29; 14%) and vertigo (3/29; 1%). After initiation of the TNF-α inhibiting therapy, neurological manifestations seldom recurred.

When focusing on stroke, it was found that a total of 25 TIAs/ischaemic strokes occurred in 12 patients. The median age at occurrence of the first TIA/ischaemic stroke was 10 years (IQR 3–27 years). Median delay between diagnosis of TIA/ischaemic stroke and diagnosis of ADA2 deficiency was 5 years (IQR 1–21). When only considering patients in whom a TIA/ischaemic stroke occurred after the first description of ADA2 deficiency in 2014, median delay between the TIA/ischaemic stroke and ADA2 deficiency diagnosis was 1 year. Of all TIA/ischaemic stroke cases, 16/25 (64%) were confirmed by MRI; the other diagnoses were based on history and neurological examination alone. No large-vessel occlusion strokes occurred in our cohort. In 3/25 (12%)

TABLE 1 General patient characteristics.

	All patients ($n=29$)	Any neurological manifestations ($n=19$)	No neurological manifestations ($n=10$)	p value[a]
Age at presentation, years, median (IQR)	5 (1–17)	4 (1–19)	8 (4–17)	0.29
Age at diagnosis, years, median (IQR)	20 (11–46)	22 (10–47)	12 (18–33)	0.80
Male sex, no./total (%)	17/29 (59)	11/19 (58)	6/10 (60)	0.91
ADA2 variants, no./total (%)				
c.506G>A p.(Arg169Gln)	10/29 (34)	8/19 (42)	2/10 (20)	NA
c.973-2A>G p.(?)	4/29 (14)	1/19 (5)	3/10 (30)	
Other variants	15/29 (52)	10/19 (53)	5/10 (50)	
ADA2 enzyme activity before therapy (U/L),[b] median (IQR)	0.3 (0.1–1.0)	0.3 (0.1–1.3)	0.3 (0.1–0.9)	0.66
Sibling pairs, no.	5	NA	NA	NA
Follow-up, years from diagnosis, median (IQR)	5 (2–8)	5 (2–8)	4 (1–6)	0.23
Mortality during follow-up, no./total (%)	5/29 (17)	4/19 (21)	1/10 (10)	0.45
Neurological manifestation at presentation, no./total (%)	9/29 (31)	NA	NA	NA
TIA/ischaemic stroke	8/29 (28)			
Cranial nerve deficit	1/29 (3)			

Abbreviations: ADA2, adenosine deaminase 2; IQR, interquartile range; NA, not applicable; no., number; SD, standard deviation; TIA, transient ischaemic attack.

[a]p value for comparison between patients with and without neurological manifestation.

[b]Missing values: $n=11$.

cases multiple vascular territories were affected at once and in 2/25 (8%) cases the vascular territory was unknown. The vascular territory that was affected most often was the brain stem and/or cerebellum (17/25 cases; 68%). The basal ganglia and/or thalamus were affected in 6/25 cases (24%) and the internal capsule in 2/25 cases (8%). There was one case of amaurosis fugax. The median number of TIAs/ischaemic strokes per affected patient was 2 (1–3). Nine patients used platelet aggregation inhibiting therapy at some time during follow-up; no hemorrhagic strokes occurred during the use of platelet aggregation inhibitors. One or more aPL antibodies were tested in 17/29 (59%) patients and in 11/12 (92%) patients with TIA/ischaemic stroke. Lupus anticoagulants were present in 4/15 (27%) tested patients and 3/10 (30%) tested stroke patients. Anti-beta 2 glycoprotein I antibody and anticardiolipin antibody levels were normal in all tested patients (12 patients and 13 patients, respectively). For most patients, no follow-up testing of aPL antibodies was done.

In 2/25 (8%) cases, a diagnosis of TIA/ischaemic stroke was made after initiation of TNF-α inhibiting therapy. The first patient was a 55-year-old male who was diagnosed with ADA2 deficiency 5 years prior. He presented with vertigo and ataxia; an MRI confirmed occipital and cerebellar lesions compatible with a recent ischaemic stroke. Two months before the stroke, TNF-α inhibiting treatment was switched from adalimumab to infliximab due to progressive non-neurological symptoms. He was tested and found negative for anti-adalimumab antibodies. As non-neurological symptoms kept recurring in the following years, despite multiple switches in and intensification of TNF-α inhibiting treatment, treating physicians consider this a case of therapy failure. The second patient was a 59-year-old male who had had two previous ischaemic strokes at ages 19 and 41 years. The third diagnosis of ischaemic stroke was made 3 years after initiation of TNF-α inhibiting therapy (adalimumab) and whilst the patient was using dual antiplatelet therapy. The stroke was localized in the posterior circulation based on clinical history and neurological examination (acute diplopia, dysarthria and gait instability), but could not be confirmed by the MRI that was performed the next day. He was not tested for anti-adalimumab antibodies. Neither patient had other known risk factors for stroke.

Two patients in our cohort had a hemorrhagic stroke. Neither patient used antiplatelet or anticoagulant therapy at the time of the hemorrhagic stroke. One had an aneurysmatic subarachnoid hemorrhage, the other a spontaneous intracerebral hemorrhage. The aneurysmatic subarachnoid hemorrhage occurred in a 29-year-old male who had suffered an ischaemic stroke 2 years prior. He presented with an acute, severe headache and slightly altered consciousness.

TABLE 2 Neurological manifestations.

	Patients with manifestation, no./total (%)	Patients with recurrence after initiation of TNF-α inhibitor, no./total (%)	Diagnosis
Headache	11/29 (38)	4/29 (14)	3/11: migraine
			8/11: other
Vertigo	6/29 (21)	3/29 (10)	3/6: TIA or ischaemic stroke
			2/6: peripheral vestibular disease
			1/6: unknown
Ataxia	5/29 (17)	1/29 (3)	5/5: TIA or ischaemic stroke
Hearing loss	4/29 (14)	2/29 (7)	2/4: TIA or ischaemic stroke
			2/4: peripheral vestibular disease
Visual loss	3/29 (10)	0/29 (0)	2/3: n. II deficit
			1/3: amaurosis fugax
Cognitive/behavioral disorder	4/29 (14)	2/29 (7)	2/4: TIA or ischaemic stroke
			1/4: depression
			1/4: ADHD, autism
Cranial nerve deficit	11/29 (38)	1/29 (3)	9/11: TIA or ischaemic stroke
n. II	2/29 (7)		2/11: n. II atrophy
n. III	6/29 (21)		1/11: Bell's palsy
n. IV	2/29 (7)		
n. VI	2/29 (7)		
n. VII	3/29 (10)		
n. VIII	2/29 (7)		
n. IX	1/29 (3)		
Seizure	1/29 (3)	0/29 (0)	1/1: acute symptomatic seizure due to ischaemic stroke
TIA/ischaemic stroke	12/29 (41)	2/29 (7)	NA
Hemorrhagic stroke	2/29 (7)	0/29 (0)	1/2: subarachnoid hemorrhage, aneurysmatic
			1/2: intracerebral hemorrhage
CNS vasculitis	0/29 (0)	0/29 (0)	NA
Peripheral neuropathy	0/29 (0)	0/29 (0)	NA

Abbreviations: ADHD, attention deficit hyperactivity disorder; CNS, central nervous system; IQR, interquartile range; n., nerve; NA, not applicable; no., number; TIA, transient ischaemic attack; TNF-α, tumor necrosis factor α.

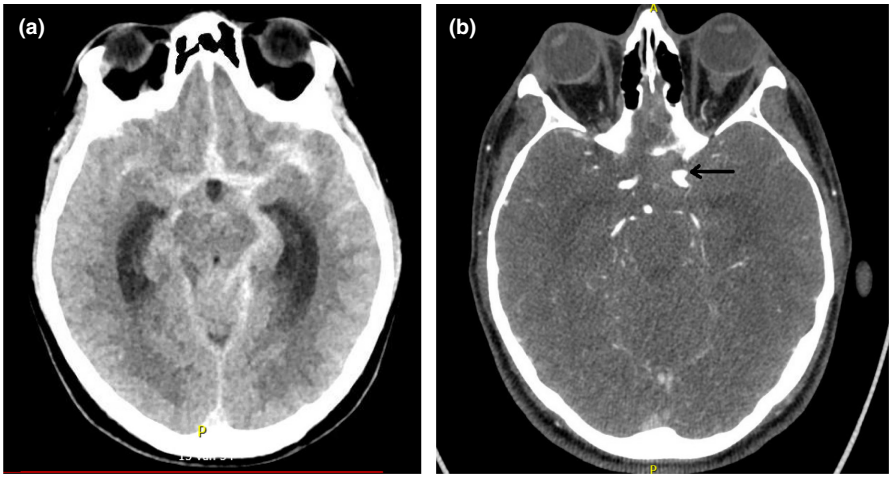

FIGURE 1 Computed tomography (CT) scan of a 29-year-old male who presented with acute, severe headache. (a) Non contrast CT (axial plane). A subarachnoid hemorrhage with hydrocephalus is shown. (b) Subsequent CT angiography (axial plane), showing a dissecting aneurysm of the left internal carotid artery (black arrow). Shortly after the subarachnoid hemorrhage, the patient was diagnosed with ADA2 deficiency.

Imaging showed a subarachnoid hemorrhage from a dissecting aneurysm of the left internal carotid artery (Figure 1). Because of hydrocephalus, the patient immediately underwent placement of an external ventricular drain. The following day, the aneurysm was clipped. An MRI did not show signs of cerebral vasculitis as a potential cause of the aneurysm. Additional imaging of the abdomen did show several small visceral aneurysms. The patient recovered without disabilities. The diagnosis of ADA2 deficiency was made shortly after the hemorrhagic stroke and treatment with a TNF-α inhibitor was initiated. The spontaneous intracerebral hemorrhage occurred in a 5-year-old female who had suffered from acute myeloid leukemia (AML) since the age of 7 months. In the years prior to the hemorrhage, she had three ischaemic strokes, attributed to the AML. This time, she presented with right-sided hemiparesis and rapidly decreasing level of consciousness. Imaging showed an intracranial hemorrhage in the basal ganglia with expansion into the ventricular system, causing midline shift and hydrocephalus. An emergency decompressive craniectomy was performed. No aneurysms were found on additional imaging. Her platelet count was normal and chemotherapy sessions had concluded several months prior. The patient recovered with a slight hemiparesis. One and a half years later, TNF-α inhibiting therapy was initiated for systemic vasculitis, and shortly after a hematopoietic stem cell transplantation was performed for her AML. The diagnosis of ADA2 deficiency was made at the age of 8 years. Whether the intracranial hemorrhage should be attributed to ADA2 deficiency, or if the patient's AML or treatment complications played a role, remains unclear.

DISCUSSION

In this study, the incidence and recurrence rates of neurological manifestations in a cohort of 29 patients with ADA2 deficiency were examined. A high frequency of neurological manifestations in ADA2 deficiency in general was observed, with TIA/ischaemic stroke being the most common. In more than a quarter of cases, TIA/ischaemic stroke was the presenting symptom.

One of our most important findings is that a substantial proportion of patients in our cohort (28%) came under medical attention for the first time because of TIA/ischaemic stroke. Unfortunately, it was not possible to distinguish between TIA and ischaemic stroke as information on symptom duration was not available for most patients. In TIA/ischaemic stroke cases that occurred after 2014, when ADA2 deficiency was first being recognized and published about, delay between the TIA/ischaemic stroke and ADA2 deficiency diagnosis was 1 year on average. This directly reflects the importance of increasing the awareness of ADA2 deficiency as a cause of young stroke amongst neurologists and pediatricians. Because it is a treatable cause of young stroke, for which antiplatelet and anticoagulant therapy are considered contraindicated, screening for ADA2 deficiency in all young patients with small-vessel ischaemic stroke without an identified cause should be advised.

Our finding that an untreated patient with a presymptomatic diagnosis of ADA2 deficiency presented with ischaemic stroke as first disease manifestation, coupled with the high frequency of TIA/ischaemic stroke as presenting manifestation in this cohort, adds to the ongoing debate on whether to initiate TNF-α inhibiting therapy to prevent ischaemic stroke in asymptomatic ADA2 deficiency patients [18]. Unfortunately, for most other patients with TIA/ischaemic stroke in our cohort, no information was available on whether they experienced any prior manifestations that were not recognized at the time but could retrospectively be attributed to ADA2 deficiency.

The frequency of TIA/ischaemic stroke in untreated patients in our cohort (41%) was very similar to the frequency described in another cohort of 60 ADA2 deficient patients [4]. However, unlike this previous study, our cohort contained two patients who were diagnosed with TIA/ischaemic stroke after initiation of TNF-α inhibiting therapy. This also stands in contrast with previous research by Ombrello et al. [19], in which 15 patients are described with a total of 733 patient-months without the occurrence of strokes after initiation of TNF-α inhibiting therapy. It underlines the need for awareness of stroke risk in these patients even after initiation of TNF-α inhibiting therapy. One patient in our cohort showed signs of anti-TNF treatment failure at the time of the recurrent stroke. Unfortunately, no data on TNF-α inhibitor drug levels in serum or repeated antibody titers were available in most patients to perform a detailed risk assessment. The recently published consensus statement on ADA2 deficiency states that hematopoietic stem cell transplantation is an effective option for pure red cell aplasia, bone marrow failure, refractory immune cytopenias, severe immunodeficiency and vascular involvement refractory to immunomodulators. Hematopoietic stem cell transplantation should therefore be considered in patients with ADA2 deficiency and recurrent TIA/ischaemic stroke after initiation of TNF-α inhibiting therapy [20].

One patient in our cohort had an aneurysmatic subarachnoid hemorrhage, which has been described previously in only one other ADA2 deficient patient [21]. The occurrence of aneurysms in these patients is most probably associated with the vasculopathy caused by ADA2 deficiency. Unlike the previously described patient, our patient also had visceral aneurysms, indicating systemic vasculopathy. It has been postulated that platelet aggregation inhibiting therapy in ADA2 deficiency patients, usually prescribed because of ischaemic stroke before the ADA2 diagnosis is established, increases the risk of intracranial hemorrhage disproportionately due to vascular fragility caused by the associated vasculopathy [4]. Although neither patient who had an intracranial hemorrhage in our cohort was on platelet aggregation inhibitors at the time of the hemorrhage, it seems rational to regard antiplatelet and anticoagulant therapy as contraindicated in ADA2 deficient patients. At best there is no expected benefit of the therapy considering the underlying pathophysiology of ischaemic stroke; at worst it might be harmful given the already increased spontaneous bleeding risk. This is of particular importance because antiplatelet and anticoagulant agents are commonly used for secondary stroke prophylaxis in patients with Sneddon syndrome [22]. Sneddon syndrome was originally described as the

concurrence of generalized livedo racemosa/reticularis and recurrent strokes, without evidence of underlying systemic disorders [23]. In later years, overlap with primary aPL syndrome was recognized, with the presence of aPL antibodies (lupus anticoagulants, anti-beta 2 glycoprotein I antibodies and/or anticardiolipin antibodies) in approximately half of patients [24, 25]. As lupus anticoagulants were found in a substantial proportion of tested ADA2 deficient patients in our cohort (27%) and that of Aksentijevich et al. [26] (41%), it is important to consider that this finding does not exclude ADA2 deficiency. It is suspected that a proportion of the patients previously diagnosed with Sneddon syndrome, even those who have aPL antibodies but do not meet the criteria for primary aPL syndrome, may in fact have ADA2 deficiency. As the therapies for these two conditions differ vastly, it is argued that caution should be exercised in diagnosing Sneddon syndrome without performing ADA2 screening.

A relatively high incidence of isolated cranial nerve deficit has been reported previously in ADA2 deficient patients [4]. However, in our cohort, most cranial nerve deficits were caused by TIAs/ischaemic strokes. One might speculate that even cranial nerve deficits without corresponding evidence of ischaemic stroke on MRI may nonetheless have a microvascular ischaemic origin, that is, disruption of the blood supply to a specific cranial nerve. Ataxia, vertigo and seizures were also most often due to a TIA/ischaemic stroke in our cohort, as opposed to being stand-alone symptoms of ADA2 deficiency. For the cases of cognitive and behavioral disorders in our cohort, it could not be determined whether these were the result of stroke or should be considered as a separate entity. Peripheral neuropathy and central nervous system vasculitis have been reported as neurological manifestations of ADA2 deficiency in previous literature [6], but overall incidence may be low as no patients in our cohort were diagnosed with either of these conditions.

In conclusion, neurological manifestations, especially TIA/ischaemic stroke, are common in patients with ADA2 deficiency and frequently are the presenting symptom. Because they are a treatable cause of young stroke, for which antiplatelet and anticoagulant therapy are considered contraindicated, awareness amongst neurologists and pediatricians is important. Screening for ADA2 deficiency in young patients with small-vessel ischaemic stroke without an identified cause should be considered.

AUTHOR CONTRIBUTIONS

Merelijne A. Verschoof: Conceptualization; investigation; writing—original draft; methodology; writing—review & editing; formal analysis; data curation. **Laura C. C. van Meenen**: Conceptualization; investigation; writing—original draft; methodology; writing—review & editing; formal analysis; data curation. **M. Valérie E. Andriessen**: Writing—review & editing. **Daniëlle M. C. Brinkman**: Writing—review & editing. **Sylvia Kamphuis**: Writing—review & editing. **Taco W. Kuijpers**: Writing—review & editing. **Helen L. Leavis**: Writing—review & editing. **G. Elizabeth Legger**: Writing—review & editing. **Catharina M. Mulders-Manders**: Writing—review & editing. **Anne P. J. de Pagter**: Writing—review & editing. **Abraham Rutgers**: Writing—review & editing. **Gijs T. J. van Well**: Writing—review & editing. **Jonathan M. Coutinho**: Writing—review & editing. **A. Elisabeth Hak**: Writing—review & editing. **Joris M. van Montfrans**: Writing—review & editing. **Femke C. C. Klouwer**: Conceptualization; investigation; writing—original draft; methodology; writing—review & editing; formal analysis; data curation; supervision.

CONFLICT OF INTEREST STATEMENT

The Eurofever Registry received unrestricted research grants. J. M. Coutinho reports grants paid to his institution from Boehringer Ingelheim, Bayer and Portola. J. M. Coutinho is a shareholder of TrianecT BV. The other authors report no individual conflicts of interest.

DATA AVAILABILITY STATEMENT

Individual patient data cannot be made available under Dutch law because patient approval was not obtained for sharing individual patient data, even in coded form. However, all syntax files and output of statistical analyses will be made available upon reasonable request.

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APPENDIX

CASE RECORD FORM

Study ID: _____

Date: __/__/____

1. Patient characteristics

1.1 Age at first presentation: ____

1.2 Age at diagnosis: ____

1.3 Mutation(s): _____
_____

1.4 Sibling with diagnosis ADA2 deficiency in Eurofever database: yes/no

1.5 Alive at time of study (April 2022): yes/no

1.6 Medication use

	Name of drug	Start date	Stop date
Platelet inhibitor			
Immunoglobulins			
TNF-α inhibitor			
Methotrexate			

1.7 Other treatments

Stem cell transplant: yes (date: _____)/no

2. Neurological symptoms/disorders

2.1 Presenting symptom(s)

|__| Neurological disorder(s)/symptom(s)

|__| Non-neurological disorder/symptom

|__| Combination of neurological and non-neurological symptoms/disorders

2.2 Neurological presenting symptoms/disorders:

|__| Headache

|__| Vertigo

|__| Ataxia

|__| Hearing loss

|__| Visual loss

|__| Cognitive/behavioral disorders

|__| Cranial nerve deficit (incl. optic neuritis and optic nerve atrophy)

|__| Seizure

|__| Transient ischaemic attack, including amaurosis fugax

|__| Ischaemic stroke

|__| Hemorrhagic stroke

|__| Central nervous system vasculitis

|__| Peripheral neuropathy

|__| Other: _____

2.3 Neurological symptoms/disorders during course of disease:

	Yes/no/ unknown	Number of episodes before start TNF-α inhibitor	Number of episodes after start TNF-α inhibitor	Additional information
Headache				Diagnosis: migraine/other:
Vertigo				Diagnosis: ischaemic stroke/other:
Ataxia				Diagnosis: ischaemic stroke/other:
Hearing loss				Diagnosis:
Visual loss				Diagnosis: optic neuritis/amaurosis fugax/other:
Cognitive/behavioral disorders				Diagnosis:
Cranial nerve deficit				Cranial nerves involved (per episode):
Seizure				
Transient ischaemic attack, incl. amaurosis fugax				Vascular territory (per episode): anterior circulation/posterior circulation/amaurosis fugax
Acute ischaemic stroke				Vascular territory (per episode): anterior circulation/posterior circulation
				Large-vessel occlusion: yes/no
Hemorrhagic stroke				Subtype (per episode): intracerebral/subarachnoid /other:
Central nervous system vasculitis				
Peripheral neuropathy				Diagnosis:

3. Diagnostic tests

3.1 Laboratory results

	Test date	Result	Unit of measurement
IgG			
IgM			
IgA			
Lupus anticoagulants			
Anti-cardiolipin antibodies			
Anti-beta 2 glycoprotein I			

3.2 Imaging

MRI(s) brain performed: yes/no

If yes, please specify:

Date: __/__/____ Findings: _____

_____

Date: __/__/____ Findings: _____

_____

Date: __/__/____ Findings: _____

_____