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CLINICAL CASE

ADA2 deficiency: case report of a new phenotype and novel mutation in two sisters

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Key messages

What is already known about this subject?
▷ ADA2 deficiency is associated with various phenotypes, from early-onset inflammation mimicking periarteritis nodosa to central nervous system involvement; cutaneous lesions are considered a key clinical feature.

What does this study add?
▷ This study extends the phenotypic spectrum of ADA2 deficiency to atypical myositis and unexplained neurological events in the absence of cutaneous involvement.
▷ Gene expression may show an interferon 1 signature but not necessarily the previously described neutrophil-associated gene overexpression.
▷ Our study emphasises the need to search for CECR1 exonic deletions in suspected cases.

How might this impact on clinical practice?
▷ In patients with persistent, early-onset inflammation, even in the absence of the most typical features, ADA2 deficiency should be considered and anti-tumour necrosis factor therapy discussed.

ABSTRACT

The objective of this paper is to: describe the phenotype compound heterozygote for mutations in CECR1 in two children. We describe the clinical and immunological phenotype, including the assessment of ADA2 activity, cytokine expression, interferon-stimulated and neutrophil-stimulated gene signatures, and the results of CECR1 sequencing. The first patient presented with intermittent fever, cutaneous vasculitis, myalgia and muscle inflammation on MRI leading to a provisional diagnosis of periarteritis nodosa. Subsequently, two cerebral lacunar lesions were identified following a brain stroke. Clinical features improved on anti-tumour necrosis factor therapy. The first patient’s sister demonstrated early-onset, long-lasting anaemia with mild biological inflammation; at the ages of 3 and 5 years, she had presented 2 acute, transient neurological events with lacunar lesions on MRI. CECR1 sequencing identified both sisters to be compound heterozygous for a p.Tyr453Cys mutation and a previously undescribed deletion of exon 7. ADA2 activity was reduced by 50%. Neutrophil-stimulated genes were not overexpressed, but interferon-stimulated genes were. The expression of a panel of other cytokine transcripts was not significantly altered. In conclusion, searching for CECR1 mutation or assessing ADA2 activity should be considered in patients with an atypical presentation of inflammatory disease.

INTRODUCTION

Loss-of-function mutations in CECR1 have recently been described in patients with vascular and inflammatory features ranging from early-onset recurrent strokes to systemic vasculitis mimicking periarteritis nodosa.1 2 While the pathological basis of ADA1 deficiency is relatively well understood, the pathogenesis of ADA2 deficiency remains unclear.3 4 A previous report suggested a possible link to an overexpression of neutrophil-derived gene transcripts.5 We describe two new cases of ADA2 deficiency in siblings with an unusual presentation, and an assessment of ADA2 activity, cytokine secretion and gene expression profiling.

MATERIALS AND METHODS

The clinical description of the two siblings was based on the medical data. Appropriate informed consent was obtained from the parents.

ADA2 activity in plasma was assessed twice, with a 3-month interval, using a commercial kit (Diazyme Laboratories). Genomic DNA was extracted from peripheral blood leukocytes using standard procedures. Exons 2–10 of CECR1 (NM_001282225.1) and flanking intronic sequences were amplified by PCR.
Cerebral MRI was normal, but a cerebrospinal fluid (CSF) pleocytosis was identified. Occurrence of another asymptomatic lacunar lesion of the disease activity 1 year later. The recent MRI showed the abnormalities resolved, with no further evidence of factor (anti-TNF) therapy (etanercept), the biological function persisted. After switching to anti-tumour necrosis factor (anti-TNF) therapy (etanercept), the biological function persisted. After switching to anti-tumour necrosis factor (anti-TNF) therapy (etanercept), the biological function persisted. After switching to anti-tumour necrosis factor (anti-TNF) therapy (etanercept), the biological function persisted. After switching to anti-tumour necrosis factor (anti-TNF) therapy (etanercept), the biological function persisted. After switching to anti-tumour necrosis factor (anti-TNF) therapy (etanercept), the biological function persisted. After switching to anti-tumour necrosis factor (anti-TNF) therapy (etanercept), the biological function persisted. After switching to anti-tumour necrosis factor (anti-TNF) therapy (etanercept), the biological function persisted. After switching to anti-tumour necrosis factor (anti-TNF) therapy (etanercept), the biological function persisted. After switching to anti-tumour necrosis factor (anti-TNF) therapy (etanercept), the biological function persisted. After switching to anti-tumour necrosis factor (anti-TNF) therapy (etanercept), the biological function persisted. After switching to anti-tumour necrosis factor (anti-TNF) therapy (etanercept), the biological function persisted. After switching to anti-tumour necrosis factor (anti-TNF) therapy (etanercept), the biological function persisted. After switching to anti-tumour necrosis factor (anti-TNF) therapy (etanercept), the biological function persisted. After switching to anti-tumour necrosis factor (anti-TNF) therapy (etanercept), the biological function persisted. After switching to anti-tumour necrosis factor (anti-TNF) therapy (etanercept), the biological function persisted. After switching to anti-tumour necrosis factor (anti-TNF) therapy (etanercept), the biological function persisted. After switching to anti-tumour necrosis factor (anti-TNF) therapy (etanercept), the biological function persisted. After switching to anti-tumour necrosis factor (anti-TNF) therapy (etanercept), the biological function persisted. After switching to anti-tumour necrosis factor (anti-TNF) therapy (etanercept), the biological function persisted. After switching to anti-tumour necrosis factor (anti-TNF) therapy (etanercept), the biological function persisted. After switching to anti-tumour necrosis factor (anti-TNF) therapy (etanercept), the biological function persisted. After switching to anti-tumour necrosis factor (anti-TNF) therapy (etanercept), the biological function persisted. After switching to anti-tumour necrosis factor (anti-TNF) therapy (etanercept), the biological function persisted. After switching to anti-tumour necrosis factor (anti-TNF) therapy (etanercep
repeated cerebral MRIs, with diffusion sequences, were normal in the acute period, which is most often associated with encephalopathy, suggestive probably of transient ischaemic strokes affecting medium and small arteries evolving later to a stroke with lacunar lesions. The clinical presentation of this patient’s sister was different. While patients have been described with only cutaneous involvement, this is the first report of a child with early stroke and no other features beyond a persistent mild inflammatory syndrome, including no cutaneous features. Hence, ADA2 deficiency should be considered as a differential diagnosis of atypical myositis or unexplained neurological events in the context of persistent inflammation, even in the absence of

Figure 1 Imaging of patient 1. (A) Muscle MRI of both legs performed at the age of 5 years: coronal gadolinium-enhanced T1-weighted sequence at different levels, showing patchy inflammatory muscular lesions. (B) Cerebral MRI performed at the age of 7 years. Left: axial gadolinium-enhanced T1-weighted sequence, showing gadolinium-enhanced mesencephalic (up) and peduncular (down) lesions. Right: axial diffusion-weighted sequence showing mesencephalic (up) and peduncular (down) hyperintensities. (C) Cerebral MRI performed 4 months later: axial gadolinium-enhanced T1-weighted sequence showing evolution towards lacunar lesions (up: mesencephalic lesions/down: peduncular lesions). (D) Cerebral MRI performed 3 years later: gadolinium-enhanced T1-weighted sequences showing lacunar lesions located in the internal capsule.

Figure 2 Illustration of the mutation and ADA2 activity. (A) Sanger sequencing analysis illustrating the point c.1358A>G mutation which was identified in both sisters. (B) Reverse quantitative PCR (RQ-PCR, copy number calculated) illustrating the exon 7 deletion in the two sisters and in the father. CECR1-E7a and CECR1-E7b are two distinct amplicons encompassing exon 7 of CECR1 gene, to avoid a possible rare polymorphism in a primer hybridisation site. (C) CECR1 mutations result in a decrease in ADA2 activity in patient plasma. The figure shows the ADA2 activity in the plasma of the two patients tested on two occasions, compared with ADA2 activity in the plasma of four controls (**p<0.001).
Finally, our patients exhibited neither hypogammaglobulinaemia nor recurrent infections, even though there were low IgM and IgA levels and mild B cell lymphopenia, in accordance with the hypothesis that ADA2 deficiency may lead to a defect in memory B cells. Interestingly, both patients also had mild biological markers of autoimmunity (ANA/lupus anticoagulant), as already reported.

While the p.Tyr453Cys mutation has been reported previously, we provide the first description of an exonic deletion of *CECR1*. This possibility should therefore be borne in mind when testing for *CECR1* mutations. Some phenotype–genotype correlations have been tentatively suggested, in particular for the G47R mutation (which might be associated less frequently with cerebrovascular involvement). However, this report and others underline the fact that marked phenotypic variability can occur even in the same family.

ADA2 enzymatic activity was reduced by almost 50% in both patients, although the clinical presentation was different. This observation indicates that ADA2 activity does not reflect the severity of the disease. We suggest that ADA2 activity dosage could be a complementary tool to diagnose ADA2 deficiency in cases where the clinical picture is suggestive and genetic testing is not conclusive (eg, in the presence of a missense variant of uncertain significance).

Gene expression analysis has already been performed in two patients with ADA2 deficiency. IFN-stimulated genes and neutrophil expressed gene overexpression have been suggested by Belot et al to be relevant to the disease phenotype. Here, an upregulation of IFN-stimulated gene expression was demonstrated in both patients, with the exception of the second sampling in the older sister. This might be partially explained by the fact that the patient did not have active disease at

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**Figure 3** IFN and neutrophil gene expression studies. The RQ value for each transcript is equal to the normalised fold change relative to a control. (A) Quantitative reverse transcription PCR of a panel of six IFN-1-stimulated genes in *CECR1* mutation-positive sisters on two occasions. IFN score was 4.82 before treatment and 1.86 after treatment in patient 1 and 11.79 and 9.47 before treatment in patient 2. IFN-stimulated genes are variably overexpressed in the two patients. (B) The expression of a panel of neutrophil-stimulated genes was measured in patients 1 and 2 on two occasions. Neutrophil-stimulated gene expression was essentially similar to that in controls. IFN-1, interferon 1; NA, not applicable; RQ value, relative quantification value.
the time of sampling and was under anti-TNF treatment. However, it is unclear to what extent the disease activity and the treatment affect cytokine transcription profiles in this disease, a point that should certainly be addressed further in future studies.

Of further note, neutrophil-derived gene expression was not elevated. It was previously hypothesised that a neutrophilic signature might explain part of the ADA2 deficiency phenotype, with a suggested role for ADA2 as plasmatic regulator of peripheral blood mononuclear cell activation. The patients described here make that possibility less likely. Meanwhile, inflammatory cytokine expression assessment did not reveal any consistent disease correlations, in accordance with previous data.

Regarding ADA2 deficiency treatment, more than 20 patients have previously received systemic therapy including anti-interleukin 1 (IL-1), without efficacy in most cases. Moreover, treatment with fresh frozen plasma and bone marrow transplantation have been proposed in regard to the protein deficiency. Furthermore, it was also reported that treatment with anti-TNF and IL-6 blockade could lead to clinical improvement (and, in the case of the former, almost normalise a previously high neutrophil signature). In our patients, short-term response to anti-TNF therapy was excellent.

To conclude, screening for CECRI mutations should be considered in patients with an atypical presentation of inflammatory disease, including myositis. Efforts to collect new cases, in particular through the Eurofever registry, may allow us to improve our disease knowledge, straddling the borders of autoinflammation and immunological deficiency. Importantly, although the pathological basis of this severe disease remains unclear, highly promising therapeutic strategies have already emerged.

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Contributors FU wrote the manuscript and followed the two children with VM for the rheumatology and the help of two neurologists EL and KD for the analyses of cerebral MRI. GS and IT performed the genetics analyses. GIR and MPR performed the ADA2 activity dosage and the interferon and neutrophil signature under the supervision of YJC. YJC also mostly participated in the correction of the manuscript. PQ contributed to all the work and especially to the correction of the manuscript.

Competing interests None declared.

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