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ORIGINAL ARTICLE

Deficiency of Adenosine Deaminase 2 Causes Antibody Deficiency

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Abstract
Purpose Determining the monogenic cause of antibody deficiency and immune dysregulation in a non-consanguineous family with healthy parents, two affected children, and one unaffected child.
Methods Whole Exome Sequencing (WES) was performed in the index family. WES results were confirmed by Sanger Sequencing. Dried plasma spots of the male patient and his mother were analyzed for ADA2 enzymatic activity.
Results Following data analysis of WES, we found a compound heterozygous mutation in *CECR1* (encoding adenosine deaminase 2, ADA2) that segregated in the two affected children. Enzyme activity measurement confirmed a severely diminished ADA2 activity in our patient. The 32 year old index patient was suffering from recurrent respiratory infections and was previously diagnosed with common variable immunodeficiency (CVID), showing no signs of vasculitis. His sister had a systemic lupus erythematosus (SLE)-like phenotype and died at age 17.
Conclusions Deficiency of ADA2 (DADA2) has been reported to cause vasculopathy and early-onset stroke. Our case suggests that it should also be considered when evaluating patients with antibody deficiencies and immune dysregulation syndromes.

Keywords Deficiency of ADA2 · primary immunodeficiency · common variable immunodeficiency · antibody deficiency · recurrent infections · systemic lupus erythematosus

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Introduction

When novel monogenic disorders are discovered, the clinical phenotype of the initial patient cohort will shape the recognition of the new disease. However, some clinical phenotypes may only be recognized over time. Deficiency of Adenosine Deaminase 2 (DADA2) has primarily been described to be associated with vasculopathy and early-onset stroke in 2014 [1–4]. Adenosine Deaminase 2 (ADA2) is an enzyme that is released to the extracellular space by monocytes, macrophages and dendritic cells. It catalyses the conversion of adenosine to inosine, but also binds directly to adenosine receptors (ADRs), proteoglycans, and other T-cell surface molecules. It is considered to help bridging cells during the immunological synapse formation [5], and is not to be confused with ADA1, which causes severe combined immunodeficiency (SCID) when defective. However, the pathogenesis of DADA2 still remains unexplained. Here, we found that DADA2 can present without vasculitic lesions, but with antibody deficiency.

Table 1 Candidate genes identified by whole-exome sequencing with compound heterozygous inheritance

CHR	Gene	Position	DBSNP ID	MAF	Location	Effect	Ref Allele	Alt Allele	Transcript ID
7	*PCLO*	82784833	rs758399155	n.a.	Exon	Insertion	T	TGCTGAGCTGGAGGCT TAGCAGGACCAAGAG	NM_014510.2
7	*PCLO*	82785097	rs61741659	0.1534	Exon	Missense	T	C	NM_014510.2
10	*PTCHD3*	27687638	rs142594066	n.a.	Exon	Missense	C	T	NM_001034842.3
10	*PTCHD3*	27702725	rs6482626	0.1985	Exon	Missense	A	G	NM_001034842.3
11	*CNTN5*	99690376	rs12292659	n.a.	Exon	Stop gained	C	T	NM_001243207
11	*CNTN5*	99690461	rs10893933	n.a.	Exon	Missense	A	G	NM_001243207
16	*TSC2*	2133701	rs5517319	0.0009984	Exon	Missense	G	A	NM_014361.3
16	*TSC2*	2138670	rs6032671; rs71744655	n.a.	3'UTR		TAA	T	NM_014361.3
22	*CECR1*	17684478	novel		Exon	Missense	A	C	NM_001282225.1
22	*CECR1*	17687997	rs77563738	0.0001997	Exon	Missense	C	T	NM_001282225.1

Chr Chromosome, *Maf* Minor allele frequency, *Ref allele* reference allele, *Alt allele* alternative allele, n.a., allele frequency was not available for this variant; transcript IDs are given for the longest transcript according to NCBI (http://www.ncbi.nlm.nih.gov/gene/?term=). All genomic positions refer to human genome build GRCh37/hg19

Methods

We were searching for the genetic defect in a non-consanguineous family with healthy parents, two affected children and one unaffected child (see Fig. 1).

Whole Exome Sequencing

Whole Exome Sequencing (WES) was performed in all five family members after taking informed consent. The sequenced reads were mapped against the human reference genome build UCSC hg19 using Bowtie 2 v2.2.3 [6], reordered, sorted and converted to bam format, followed by the removal of polymerase chain reaction (PCR) duplicates with Picard v1.115. Local realignment around insertions and deletions (InDels) and base quality score recalibration as well as variant calling and variant quality score recalibration were performed with the Genome Analysis Toolkit (GATK) v3.1 [7] according to their best practice recommendations. Analysis of genetic variant data in the

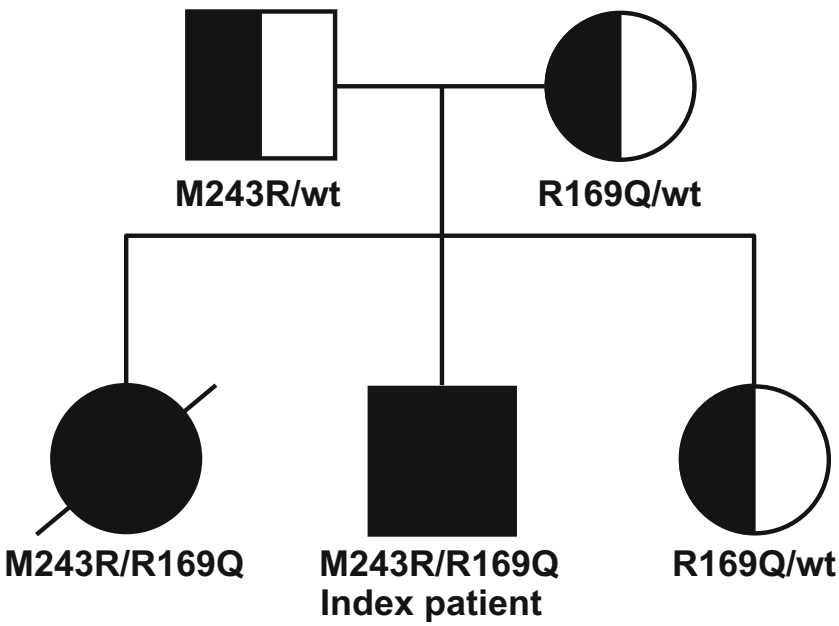

Fig. 1 Pedigree of the index family. Mutations in *CECR1* identified by WES are depicted underneath the symbols. wt = wild type

Table 2 Candidate genes identified by whole-exome sequencing with homozygous inheritance

CHR	Gene	Position	DBSNP ID	MAF	Location	Effect	Ref Allele	Alt Allele	Transcript ID
1	*PYHIN1*	158946658	rs145640162	n.a.	3'UTR		CTATATATATATATA TATATATATATATA	C	NM_152501.4
2	*PIKFYVE*	209220157	rs10208191	n.a.	3'UTR		G	T	NM_015040.3
2	*SPAG16*	214182100	rs10183630	n.a.	3'UTR		A	T	NM_001025436.2
2	*TNSI*	218695102	rs3796028	n.a.	Exon	Missense	G	A	NM_022648.4
2	*TNSI*	218713282	rs3796033	n.a.	Exon	Missense	G	A	NM_022648.4
6	*TCP10L2*	167592524	rs2989545	n.a.	Exon	Missense	T	C	NM_001145121.1
10	*SPOCK2*	73848105	rs10713496; rs398046069	n.a.	5'UTR		TG	T	NM_014767.2
10	*PNLIPRP2*	118397884	rs4751995	n.a.	Exon	Missense	A	G	NM_005396.4
10	*PNLIPRP2*	118404620	rs2301179	n.a.	3'UTR		A	G	NM_005396.4
11	*TRAPPC4*	118889247	rs11440855	0.0000	5'UTR		A	AG	NM_016146.4
15	*AQR*	35261952	rs7164070	n.a.	5'UTR		C	T	NM_014691.2
19	*LILRB1*	55148249	rs16985478	n.a.	Exon	Missense	G	A	NM_006669.5

Chr Chromosome, *Maf* Minor allele frequency; *Ref allele* reference allele, *Alt allele* alternative allele; n.a., allele frequency was not available for this variant; transcript IDs are given for the longest transcript according to NCBI (http://www.ncbi.nlm.nih.gov/gene/?term=). All genomic positions refer to human genome build GRCh37/hg19

form of Variant Call Format (VCF) files was conducted using the VCF tools program package [8]. For the annotation of variants with the IDs from the short genetic variants database dbSNP v144, we used SnpSift, which is part of the main distribution of the toolbox SnpEffv3.6 [9]. The annotation of variants with the genes and transcripts they are effecting and the effects they produce (e.g. whether they hit exons) were conducted using effect prediction tool SnpEff. The common variants (frequency > 0.01 in dbsnp144) were then eliminated. Genes were designated as related to the immune system as previously described [10]. All known gene defects associated with common variable immunodeficiency (CVID) were ruled out with the help of the WES data. Homozygous and compound heterozygous candidate variants (see Tables 1 and 2) were prioritized according to frequency, a reported function in the immune system, and software predictions for a possible damaging effect of the variant [11, 12].

Sanger Sequencing

WES results were confirmed by Sanger Sequencing. Coding genomic regions including flanking intronic sequences of *CECR1* were amplified from genomic DNA by standard PCR. PCR primers were used for Sanger sequencing according to standard techniques. Primer sequences are available on request.

ADA2 Activity Measurements

Plasma prepared from EDTA anti-coagulated blood obtained from the male patient, his mother, and a healthy control was applied to circles of Guthrie filter cards and allowed to dry before being sent to Duke University. ADA2 activity was then measured in extracts of the dried plasma spots using the HPLC method described by Zhou et al. [2] As the dried plasma spot method is still in development (SJ Kelly, NJ Ganson, MS

Table 3 ADA2 activity in dried plasma spots

Source of samples	Dried Plasma ADA2 activity [mU/g plasma protein]	Dried Plasma ADA2 activity [mU/g plasma albumin]
Male patient	2.0	3.0
Patient's mother	46.1	72.0
Healthy control	82.8	127.4
ADA2 deficient patients ($N = 4$)	2.8 ± 0.7 (2.0–10.1)	4.4 ± 1.5 (3.0–14.0)
ADA2 carriers ($N = 6$)	73. 9 ± 25.7 (42.1–108.7)	132.9 ± 40.2 (72.0–164.3)
Healthy controls ($N = 4$)	155.3 ± 88.1(82.8–270.6)	342.6 ± 165.3(127.4–496.9)

Hershfield unpublished), ADA2 activity was normalized to both total protein and albumin in the extracts (see Table 3).

Results

The Patients Presented with Immunodeficiency and Immune Dysregulation

The currently 32-year old index patient presented at age 18 with recurrent infections of the upper respiratory tract, mouth ulcers, and intermittent pain in the metacarpophalangeal joints of his hands. He was found to have splenomegaly. He had two episodes of pneumonia in childhood and a third one at age 18 (see Fig. 2). He suffered from asthma since age seven. He also reported chronic diarrhea. Laboratory findings showed a selective IgA deficiency (<0.23 g/L). This was confirmed at age 19 along with a lack of production of IgG2, IgG3 and IgG4. When next presenting at age 24, overall IgG levels were markedly decreased (IgG 3,95 g/L), indicating a progressive loss of IgG. Hence, the diagnosis of common variable immunodeficiency (CVID) was established. IVIG (intravenous immunoglobulin) and later on SCIG (subcutaneous immunoglobulin) treatment were started, but compliance was low. Presenting again at age 31, his IgG levels had fallen to 2.08 g/L. He reported recurrent respiratory infections with fever. IVIG substitution was started again and has prevented further episodes of infections. Neither clinical examination nor magnetic resonance angiography showed any signs of vasculitis. Original ESID/PAGID (1999) criteria [13] as well as the updated ESID 2014 criteria (http://esid.org/Working-Parties/Registry/Diagnosis-criteria) for CVID diagnosis were fulfilled, as he had an increased susceptibility to infection, antibody deficiency, absent vaccine responses to pneumococcal polysaccharide and diphtheria, and low switched memory B cells (3.6 %, normal range (NR): 6.5–29.2 %). Secondary causes of hypogammaglobulinemia (such as protein-loss, lymphoma and drug induced humoral deficiency) were excluded as well as a profound T-cell deficiency (by T-cell phenotyping).

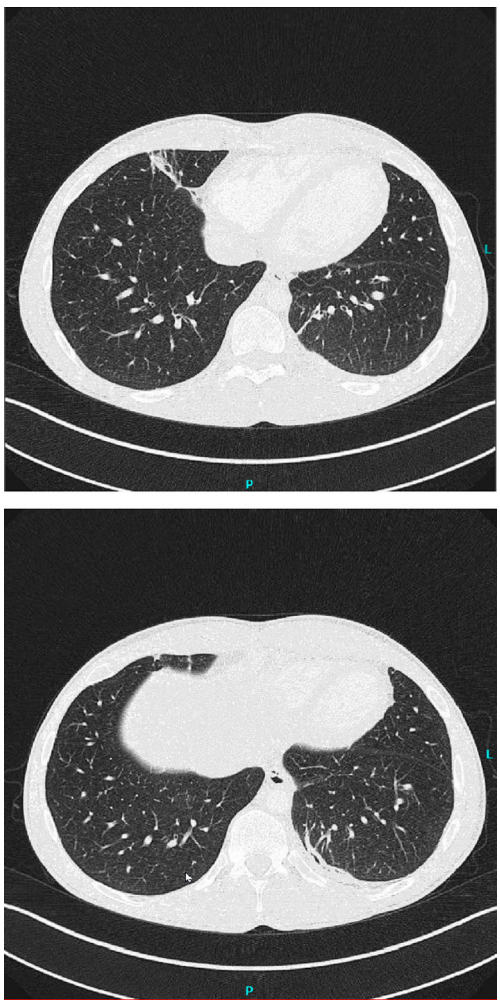

Fig. 2 CT scan of the male patient's lung. The CT scan shows post-inflammatory changes

The index patient's sister started to have erythema nodosum-like skin lesions on her shins at age two years. During infancy, she suffered from recurrent urinary tract infections. At age six she had a Gregoir-anti-reflux-operation on her left kidney due to congenital hydronephrosis, two episodes of scarlet fever, developed splenomegaly, and was diagnosed with microcytic hypochromic anemia. Starting age 10 she had recurrent bouts of fever, arthritis, and erythema nodosum. Symptoms resolved spontaneously after several weeks. Rheumatic factor, ANA and dsDNA antibodies were negative at age 13. At age 12 she had episcleritis and tonsillectomy, following recurrent streptococcal infections. She had failure to thrive and a delayed sexual development. At age 14, she underwent nephrectomy of her left kidney. Histology showed a severe lymphocytic and granulomatous interstitial nephritis and lymphocytic vasculitis, but there were no hallmarks of an immune complex-mediated disease (see Fig. 3). Histologically, those features could not be attributed to a known systemic disease. Methotrexate-therapy and oral steroids improved her symptoms but were unable to induce full remission. At age 14, she was diagnosed with hypogammaglobulinemia and received IVIG treatment. At age 16, elevated C3d was confirmed, but no immune complexes were detectable, possibly due to her antibody deficiency. Skin involvement, nephritis, arthritis, and lymphopenia suggested systemic lupus erythematosus (SLE) as differential diagnosis according to the American College of Rheumatology SLE criteria [14], but low antibody titers and absent vaccine response to diphtheria and tetanus hinted towards CVID. She was splenectomised aged 17, having cellular pooling due to her splenomegaly. Histological examination of the spleen showed fibrotic foci hinting at previous infarctions. Examination of hilar lymph

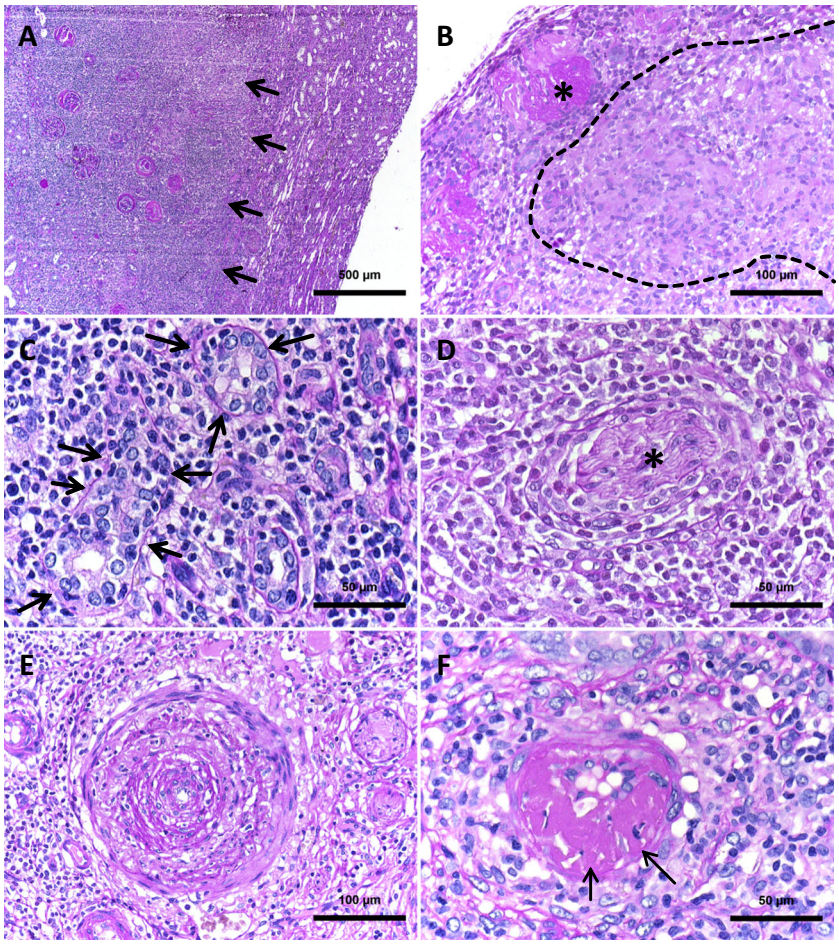

Fig. 3 Histology of kidney inflammation. **a** Dense cortical inflammatory infiltrate with severe glomerular scarring and effacement of tubular structures (*arrows* mark corticomedullary junction). Most of the inflammatory cells consist of lymphocytes. **b** Multiple epitheloid cell aggregates and non-necrotizing granulomas are situated in the interstitium (separated by *dotted line*). The majority of glomeruli is scarred (*asterisk*). **c** Lymphocytic tubulitis (*arrows* mark tubular basement membrane). **d** Lymphocytic perineuritis (nerve marked by *asterisks*). **e** Severe lymphocytic vasculitis, leading to focal fibrinoid necrosis of the arterial wall (**f**). PAS staining in all pictures, magnifications as indicated by *bars*

nodes demonstrated the presence of a lymphocytic vasculitis (see Fig. 4). Three months later, she developed cerebral bleeding leading to an incarceration in the tentorial notch (see Fig. 5), and multiple organ failure following pneumoni a. Candida and Pseudomonas were cultured. She died in 1999 at the age of 17. Both parents as well as another sister were healthy.

WES, Sanger Sequencing and ADA2 Activity Measurements Led to the Diagnosis of DADA2

Before moving to WES, defects in TACI, ICOS, BAFF-R, APRIL, EAT2, IL10RB, XIAP, BAFF, CCL18, IL21, BOB1, IL10, IRF4, BCMA and IL10RA had been ruled out by targeted Sanger Sequencing. HLA-B27 was negative in the index patient's sister. All known CVID candidate genes were excluded on the basis of WES Data. Data analysis revealed a heterozygous, non-synonymous missense-mutation in *LRBA* in the two affected children. However, it was considered unlikely to be the disease causing mutation due to its inheritance pattern, as the healthy mother was also carrying the mutated allele. Instead, we focused on homozygous and compound heterozygous mutations, as the parents were both healthy (see Tables 1 and 2). We found two point mutations leading to an amino exchange in *CECR1* (encoding ADA2) that perfectly segregated in the family. The affected siblings were compound heterozygous for both mutations, whereas the parents and the healthy sister were carriers of only one mutation. The first mutation Chr22:17687997C > T causes a change from arginine at position 169 to glutamine and has been reported as disease-associated earlier [1, 2]. This highly conserved amino acid in the putative receptor binding domain of ADA2 is listed as a SNP (single nucleotide polymorphism; rs77563738) with a minor allele frequency (MAF) of 0.0002 %. The second mutation in *CECR1* (Chr22:17,684, 478 A > C) leads to a change from methionine at position 243 to arginine and is a novel mutation, located in the catalytic domain of the ADA2 enzyme. Prediction tools (Mutation taster, Provean and SIFT) predicted both mutations to be disease-causing or damaging. Analysis of dried plasma spots showed a severely diminished enzymatic activity of ADA2 in the index patient (see Table 3). His mother had ADA2 activity levels in the range of other carriers of one mutated allele. The Table also shows mean ± sd (range) for ADA2 activity in dried plasma spots prepared in the same manner at Duke from previously studied ADA2-deficient

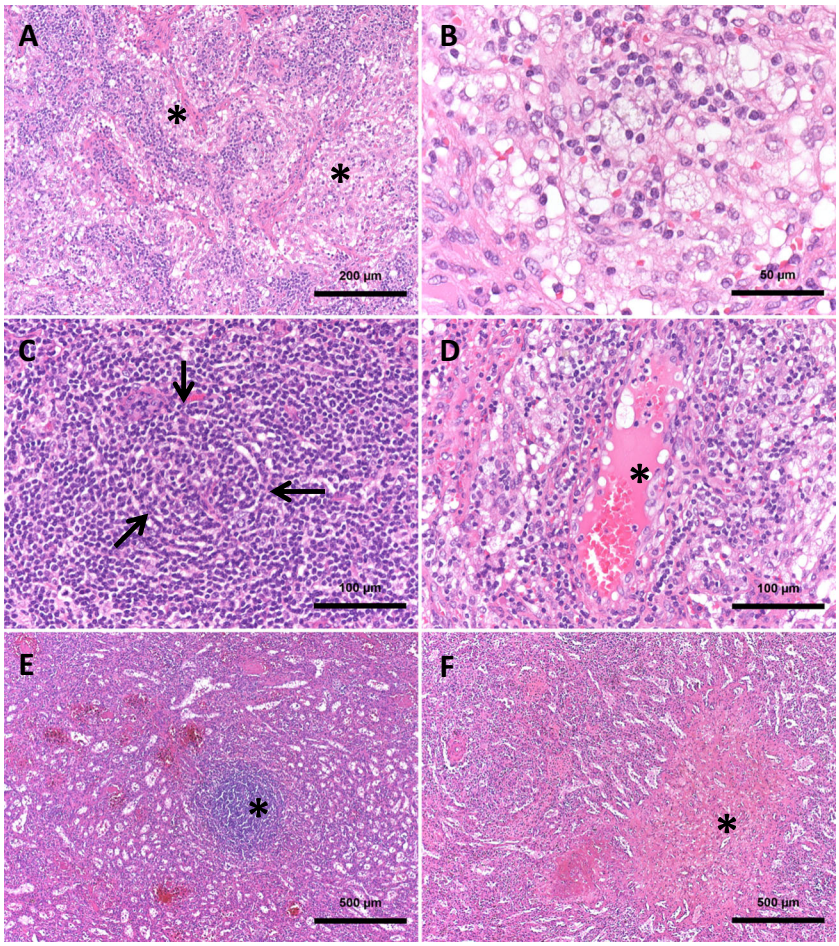

Fig. 4 Histology of hilar lymph nodes and spleen. **a** Lymph nodes show dilated sinusoids (*asterisk*) with multiple foamy macrophages, which are highlighted in higher magnification in (**b**). **c** Very sparsely, small follicles can be found (highlighted by *arrows*). **d** Lymphocytic vasculitis in a small artery of the lymph node (lumen highlighted by *asterisk*). **e** Diminished white pulp of the spleen (lymphoid aggregate highlighted by *asterisk*) and focal scarring (**f**, *asterisk*) can be found as well as dilated sinusoids. H&E staining in all photomicrographs, magnifications as indicated by *bars*

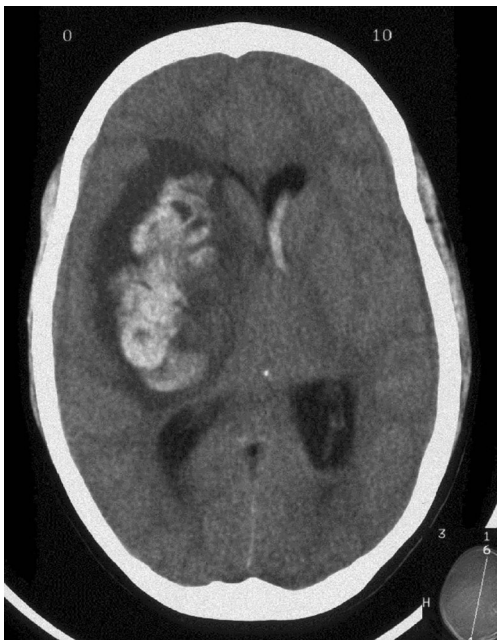

Fig. 5 CT scan of the female patient's brain. The CT scan demonstrates an intracerebral space-consuming bleeding with midline shift

patients, known carriers, and healthy controls, as indicated. The patient's ADA1 activity (measured in dried whole blood spots) was normal. Total deoxyadenosine nucleotides levels in dried blood spots were not detectable (NR < 1 %). Therefore, the diagnosis of deficiency of ADA2 (DADA2) was established for the male patient and can be assumed for his deceased sister, according to her genotype.

Discussion

Compared to skin manifestations and vasculopathy, less attention has been paid to the immunological features of DADA2 patients, and the clinical manifestations of immunodeficiency seem to be quite variable between cohorts and individual patients. In the NIH cohort, patients were reported to have fewer memory B cells in the peripheral blood, and lower expression of CD27 and IgG on B cells upon stimulation. [2], whereas those immunological features are not mentioned in the paper on the Georgian Jewish cohort. [1] Out of the 54 DADA2 patients reported so far [1–4, 15–18], eight were diagnosed

with hypogammaglobulinemia and one with selective IgM deficiency. Intriguingly, two recently reported DADA2 patients had increased levels of IgG [18]. However, they were also deficient for IL17 Receptor A, and can therefore not be compared directly with the other DADA2 patients. Among the ones with hypogammaglobulinemia were also two siblings who had not only low memory B cells, but also aspects of combined immunodeficiency, autoimmunity, and lymphoproliferation [15]. Snedden's Syndrom and Castleman-like disease have also been discussed as possible DADA2-phenotypes [16].

Neither the cause of the vasculitis, nor the defects in the adaptive immune system in DADA2 have been explained so far. The ADA2 protein is not expressed in cultured human endothelial cells [2], nor in any blood cells apart from monocytes, macrophages and dendritic cells [5]. This hints towards more complex mechanisms leading to endothelial damage and immunodeficiency in DADA2 patients, possibly related to the chronic inflammatory condition intrinsic to DADA2.

With the phenotype of the disease expanding, the cohorts to be screened for DADA2 should be broadened accordingly. We suggest to screen CVID patients with vasculitic manifestations, but also those with unexplained high CRP levels. When screening SLE patients for ADA2 mutations, uncommon forms like the absence of auto-antibodies, hypogammaglobulinemia or selective immunoglobulin deficiency and the occurrence of cerebral lesions should be especially taken into account. Familiar clustering always hints towards a genetic background.

Conclusion

Here, we found that DADA2 can present clinically as common variable immunodeficiency or atypical systemic lupus erythematosus. Antibody deficiencies and immune dysregulation syndromes should be put on the possible spectrum of clinical presentations of DADA2. A typical manifestation of DADA2 is an uncommon form of vasculitis that cannot be classified as a typical trait of a known systemic disease so far. Here, we present the histology of DADA2 kidney vasculitis for the first time, which could guide pathologists facing this new disease. Moreover, we suggest that measuring of ADA2 activity in extracts of dried plasma spots can be used as a rapid and reliable diagnostic test.

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Our dear collaborator Dr. Wilma Mannhardt-Laakman died in December 2015. We want to thank her for her dedication to caring for this family and so many other children with rheumatological and immunological conditions. We would like to dedicate this publication to her.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval 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.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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