Title: Inflammatory Myopathy in a Patient with Aicardi-Goutières Syndrome

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Running title: Inflammatory myopathy in Aicardi-Goutières syndr.

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Abstract: Aicardi–Goutières syndrome (AGS) is an inflammatory disorder belonging to the recently characterized group of type I interferonopathies. The most consistently affected tissues in AGS are the central nervous system and skin, but various organ systems and tissues have been reported to be affected, pointing to the systemic nature of the disease. Here we describe a patient with AGS due to a homozygous p.Arg114His mutation in the *TREX1* gene. The histologically proven inflammatory myopathy in our patient expands the range of clinical features of AGS. Histological signs of muscle biopsies in the proband, and in two other AGS patients described earlier, are similar to those seen in various autoimmune myositises and could be ascribed to inapproapriate IFN I activation. In view of signs of possible mitochondrial damage in AGS, we propose that mitochondrial DNA could be a trigger of autoimmune responses in AGS.

Key words: inflammatory myopathy, Aicardi-Goutières syndrome, type I interferonopathy, autoimmune myositis, exome sequencing.

Introduction

Aicardi–Goutières syndrome (AGS) is an inflammatory disorder caused by mutations in any of seven genes involved in nucleic acid metabolism/signaling and belonging to a recently characterized group of inborn errors of immunity termed type I interferonopathies [1]. The hallmark of these diseases is an inapproapriate up-regulation of type I interferon (IFN I) with further induction of IFN I-mediated innate and adaptive immune responses. Increased expression of IFN I-stimulated genes in serum and cerebrospinal fluid, so-called IFN I signature, was observed in 90% (74 of 82) of patients with mutation-proven AGS [2]. Four human diseases were associated with *TREX1* mutations, including Aicardi-Goutières syndrome 1 (OMIM #225750), familial chilblain lupus (FCL, OMIM #610448), systemic lupus erythematosus (SLE, OMIM #152700), and retinal vasculopathy with cerebral leukodystrophy (OMIM #192315) [3]. The most severe of these nosologies, AGS1, can encompass the features of both FCL and SLE [1,4,5]. Correspondingly, families segregating both FCL and AGS through several generations have been described [6]. SLE was the first human disease consistently associated with increased levels of IFN I and IFN I signature [7]. Moreover, activation of the IFN I pathway in the blood and affected tissues has been found in a vast variety of systemic autoimmune diseases, including systemic sclerosis, Sjögren's syndrome, dermatomyositis, polymyositis, and rheumatoid arthritis [7,8,9,10]. All these disorders can present considerable clinical overlap and affect almost any human organ or tissue [7].

The most consistently affected tissues in AGS are the central nervous system and skin, but a vast range of clinical features in various organ systems and tissues have been reported, pointing to the systemic nature of the disease [1,5]. Here we describe a patient with histologically proven inflammatory myopathy and AGS due to a homozygous p.(Arg114His) missense variant in the *TREX1* gene. Correlation with earlier published cases of muscle biopsy

investigations in AGS and with histopathological signs of autoimmune myositis is provided with suggestions concerning possible common pathogenetic mechanisms in all these human pathologies.

Case report

The proband, an 11-year-old female at the time of diagnosis, was the youngest child of healthy unrelated Lithuanian parents. Although she had two older healthy male and female siblings, her oldest brother died at the age of 2.5 months with a presumable, though not laboratory-confirmed, perinatal infection, neonatal seizures, and focal brain lesions in neurosonoscopy. She was born at term with birth weight and birth length in the 50th and the 75th centile respectively and occipitofrontal head circumference (OFC) in the 3rd centile (32 cm). She had an uneventful postnatal period and was considered healthy until the age of three months, but retarded early psychomotor development milestones such as lack of a smile and head lag were reported retrospectively. At the age of three months, she became extremely irritable, with inconsolable crying, pyrexia, feeding difficulties, infantile spasms, and marked startle reactions provoked by acoustic, tactile and other stimuli. Multiple brain calcifications were observed in a head CT already at that age. Developmental regress with progressive microcephaly and failure to thrive became evident. She subsequently developed spastic tetraparesis with truncal hypotonia, blindness with pale optic nerve discs, and cardiac arrhythmia, with episodes of paroxysmal supraventricular tachycardia, multifocal extrasystoles, and atrioventricular/sinoatrial heart block with normal findings on echocardiography. Right eye and subsequently left eye glaucoma developed at the age of nine and ten years. Sensorineural hearing loss was diagnosed at the age of two years. Episodes of sterile pyrexia lasting one to two days were observed three to eight times per year, with increasing frequency at the age of

twelve to thirteen years of age. The patient suffered several episodes of pneumonia during her life. Chilblain lesions on her toes and feet appeared at the age of 11 years and increased in frequency at the age of twelve years. She also developed severe kyphoscoliosis and contractures of her knees, ankles and elbows and generalized muscle atrophy, as well as being of short stature and hypotrophic. The patient had severe intelectual disability with absent psychosocial and motor functions. Epileptic spasms and startle reactions provoked by acoustic stimuli were observed several times per day. At the age of 6 years, electroencephalographic records showed a slow disorganized background with intermittent spikes and sharp waves, more pronounced frontotemporally on the right. At the age of 11 years, groups of spikes over the right parietooccipital, deformed complexes of spikes and waves, and high *theta* waves over the right parietotemporal regions were registered in an EEG. Multiple confluent calcifications periventriculary, subcortically, in the basal ganglia, and in the cerebellar white matter and marked diffuse cerebral and cerebellar atrophy were observed in a head CT at the age of 11 years. She had never had any endocrinological abnormalities. The patient developed severe dysphagia necessitating gastrostoma, respiratory insufficiency, increasingly frequent pyrexias, and chilblain lesions and passed away at the age of thirteen years (figure 1).

Figure 1 (A and B). Phenotype of the patient at the age of 11 years: marked atrophy of facial and dorsal interosseous muscles, microcephaly, convex nasal bridge, and retrognathia.

Genetic counseling with subsequent genetic testing were provided to the proband at the age of 11 years. Blood and urine tests for inborn errors of metabolism and karyotyping did not demonstrate any diagnostic abnormalities. Muscle biopsy, except from several isolated cytochrome oxidase (COX)-negative fibers, failed to reveal signs suggestive of primary

mitochondrial diseases. Marked perivascular inflammatory infiltrates with lymphocytes and isolated plasmocytoid dendritic cells, not extending into the endomysium, were however observed (Figure 2). There was ubiquitous up-regulation of MHC-I expression in otherwise structurally normal muscular fibers. To uncover genetic variants associated with the abnormalities shown by the proband, we performed whole exome sequencing of DNA extracted from her blood, her parents, and her two healthy siblings as previously described [11,12]. Briefly, exomes were captured using the Agilent SureSelect Human All Exon V5 enrichment kit and multiplex sequenced on an Illumina HiSeq 2500 platform. Variants were filtered according to the quality of the calling, their frequency in control populations, their adherence to either being *de novo* in the proband or with an autosomal recessive inheritance pattern, and their predictive impact on the function of the protein (see Supplementary methods, Supplementary Table S1). Five variants in four genes, all confirmed by Sanger Sequencing, complied with these filtering steps (Supplementary Table S2). We uncovered in particular that the proband was homozygote for a known pathogenic variant in *TREX1* (NM_033629.4:c.341G>A; NP_338599.1:(p.Arg114His)). This variant has an allele frequency of 0.00016 in ExAC Version 0.3 (http://exac.broadinstitute.org/). It is the most common of the known pathogenic *TREX1* variants, being found in 35 out of 70 (50%) of parents of Northern European ancestry with AGS due to *TREX1* mutations [1]. These findings allow us to hypothesize that the deceased elder brother was homozygous for the same variant, as his clinical features matched AGS.

Figure 2. Quadricep muscle biopsy with isolated COX-negative fibers (**A**), perivascular inflammatory infiltrates with lymphocytes and isolated plasmocytoid dendritic cells, not extending into the endomysium (**B**), and homogenous ubiquitous up-regulation of MHC-I expression in otherwise structurally normal muscular fibers (**C**).

Discussion

Type I interferons play a pivotal role in the immune response to infection by influencing development of innate and adaptive immune responses. The outcomes of IFN I responses can however vary from clearing out the pathogens to chronic infection and autoimmune diseases [13]. One of the causes of recently ascribed to type I interferonopathies Aicardi-Goutières syndrome is a genetic alteration in the *TREX1* gene encoding the major mammalian and ubiquitous *3'-5'* DNA exonuclease [1,14]. Though AGS is mostly considered to be a neurological disorder with onset in the neonatal period or early childhood and mostly stable disease course after the first episode of acute or subacute illness, it is known to affect multiple tissues and organs, including the skin, endocrinological and gastrointestinal systems, and heart. However, persistent throughout the whole life of patients and progressive, disease process was suggested because of the persistently found up-regulation of IFN-I induced genes (IFN I signature) and recurrent episodes of fever and chilblains [1,15]. Features or histological signs of inflammatory myopathy were not mentioned in earlier reports of AGS patients, but it is difficult to ascertain skeletal muscle damage in a profoundly disabled child with absent or severely disturbed motor functions. Of note, signs of myopathy in electromyography were observed in a child with AGS [16]. Also, 3.3% of AGS cases from a large cohort of 374 patients had infantile-onset hypertrophic cardiomyopathy [1]. *Trex1*$^{-/-}$ mice exhibit reduced survival and develop inflammatory myocarditis leading to progressive cardiomyopathy. Focal lymphoid aggregates were also seen in murine liver, lungs, and other tissues [17].

There are several reports of muscle biopsies performed in AGS patients. A patient with a *de novo* heterozygous p.(Asp18Asn) mutation in the *TREX1* gene and a mild presentation of AGS syndrome was found to have isolated ragged red fibers, COX-negative fibers, and

decreased overall energy (ATP and creatine phosphate) production in the presence of normal activities of the individual respiratory chain complexes [16]. Southern blot analysis of muscle tissues from an affected child and two affected fetuses demonstrated multiple mtDNA deletions in a family with AGS5 (OMIM#612952) due to a large homozygous deletion of the *SAMHD1* gene [18]. There is no mention of any inflammatory signs in muscle biopsies in these cases. Interestingly, ragged red fibers, COX-negative fibers, and multiple mitochondrial DNA deletions are frequent findings in inclusion body myositis, a progressive autoimmune disorder with an insufficiently evaluated etiopathogenesis [19]. Autoimmune myositis with inflammatory infiltrate in muscle biopsy is a constant feature of other diseases such as dermatomyositis and polymyositis and occurs with increased frequency in patients with other systemic autoimmune diseases, including systemic lupus erythematosus (SLE) [19]. Perivascular and perimysial inflammatory infiltrates were recently found in 46% of biopsied patients (7 of 15) with SLE [20]. Interestingly, no correlation with clinical features or serological signs was observed. Perivascular inflammatory infiltrates of lymphocytes and dendritic plasmocytes is a constant histological feature of dermatomyositis [8,19]. Plasmacytoid dendritic cells are the main producers of IFN I, and all these disorders were shown to be associated with an IFN I signature [7,8,9,21].

It is well known that the accumulation of cytosolic nucleic acids activates the IFN I response [14,22]. The precise trigger of the IFN I response in AGS is unknown, and there are hypotheses implicating metabolites of DNA replication and repair [23] or fossil genome retroelements in IFN I activation [14,24]. Almost half of the human genome consists of retroelements and many of them are still active. The origins of the disease in a substantial proportion of patients have a prenatal onset (22.8%) in the biggest cohort to date of 374 AGS patients [1] when confrontation with exogenous sources of nucleic acids is limited.

Interestingly, treatment with three reverse transcriptase inhibitors in doses comparable to those given to patients with HIV substantially reduced mortality and inflammatory myocarditis in *Trex1*$^{-/-}$ mice, further pointing to the role of genome retroelements in the activation of autoimmunity [25]. However, since mitochondria are evolutionary endosymbionts containing DNA similar to bacterial DNA, there is a possibility that mitochondrial DNA could be an additional trigger of autoimmunity. Indeed, as was recently shown, mitochondrial DNA that escapes from autophagy cells autonomously leads to Toll-like receptor (TLR) 9 mediated inflammatory responses in cardiomyocytes and is capable of inducing myocarditis and dilated cardiomyopathy [26]. There is a possibility that a secondary mitochondrial damage as evidenced by ragged red fibers, COX-negative fibers, and multiple DNA deletions in skeletal muscle biosies of AGS patients [16,18] and accumulating mitochondrial DNA are further activators of autoimmune responses in AGS.

In conclusion, histologically proven inflammatory myopathy in our patient expands further the range of clinical features in AGS syndrome. Histological signs of muscle biopsies in our patient and in two other genetically confirmed AGS patients described earlier are similar to those seen in various autoimmune myosites and could be ascribed to a common pathogenetic mechanism of inapproapriate IFN I activation. Fossil genome retroelements and other substrates of TREX1 such as metabolites of DNA replication and repair have been suggested as a possible trigger of autoimmune responses in AGS; in view of signs of possible mitochondrial damage in AGS and a recent publication linking accumulated mitochondrial DNA with autoimmune myocarditis, we propose that mitochondrial DNA could be another trigger of autoimmune responses in AGS. However, the latter hypothesis warrants further evaluation.

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Declaration of Conflicting Interests

The authors declare no conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

The Regional Research Bioethics Committee approved this study. All study participants provided written informed consent.

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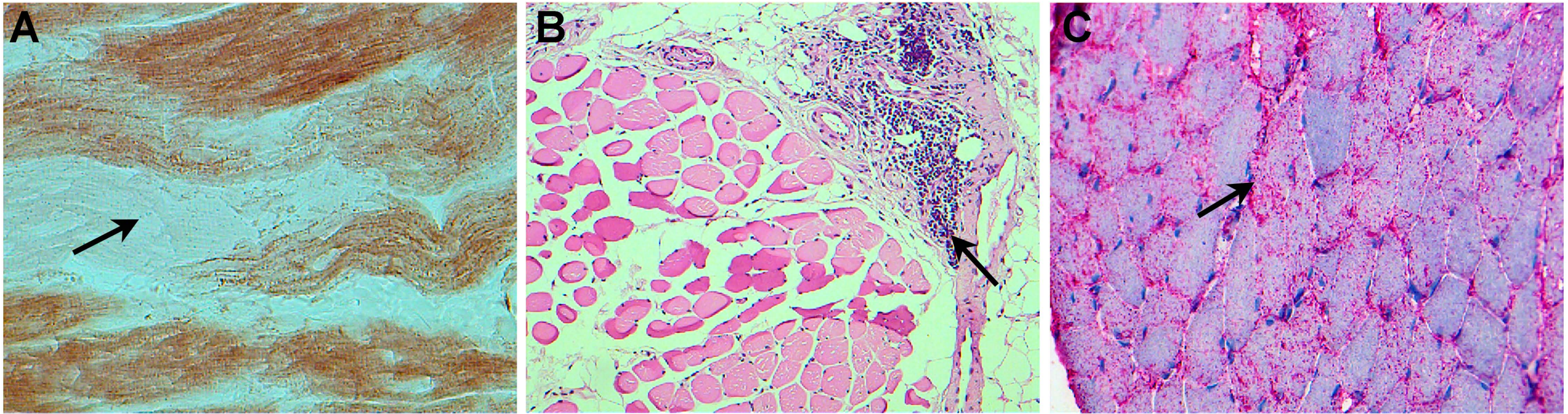
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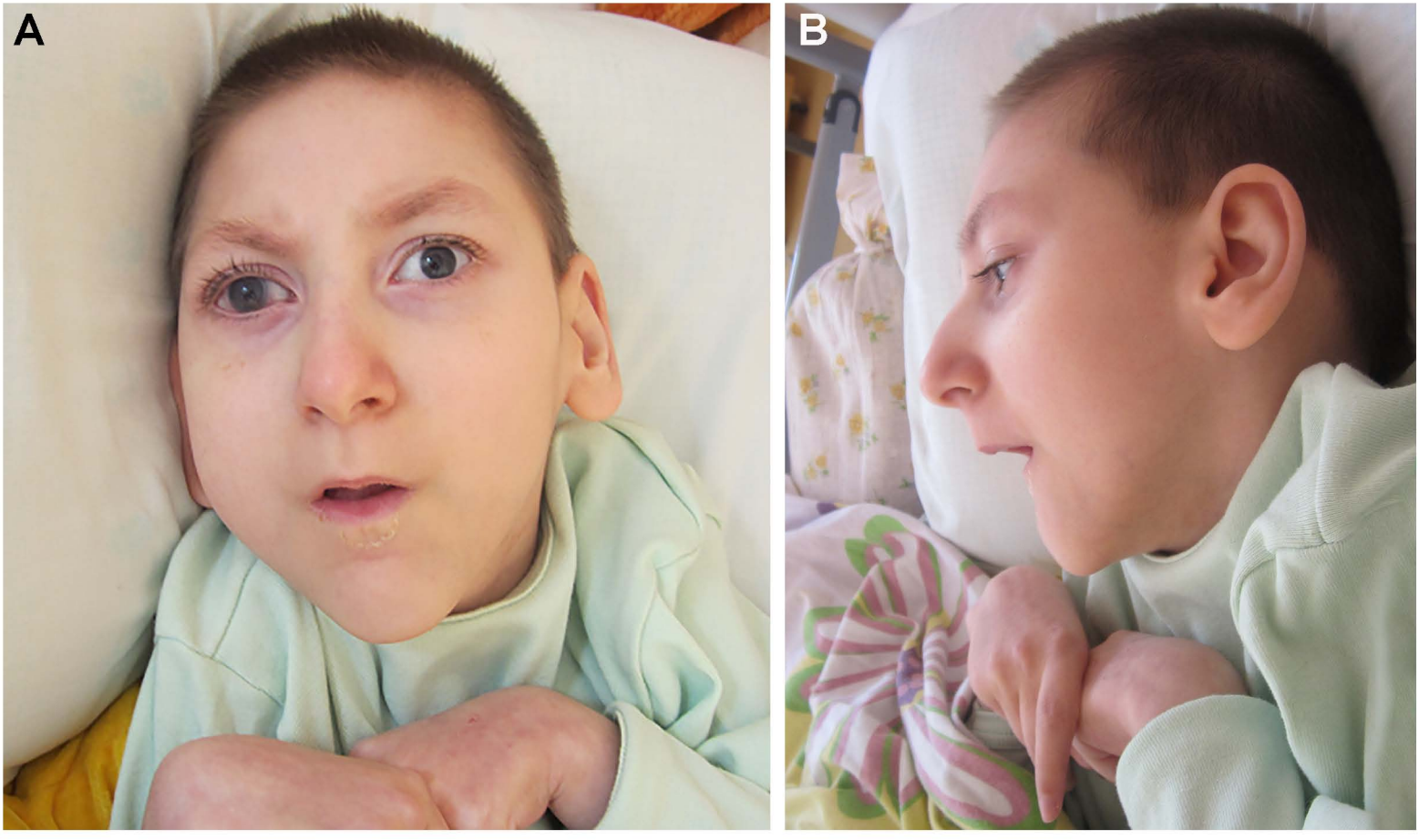
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