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Aicardi-Goutières Syndrome: A Case Report

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Article Summary: A case report of a 22-month-old male with Aicardi-Goutières Syndrome that was diagnosed at four months of age after an episode of status epilepticus.

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Abstract

Background: Aicardi-Goutières Syndrome (AGS) is a rare genetic neurological disorder that presents as pseudo-TORCH syndrome. There are 350 confirmed cases worldwide. This case report describes a 22-month-old male with Aicardi-Goutières Syndrome who was diagnosed at four months of age. This paper seeks to highlight AGS as a differential for TORCH Syndrome, and to build on the limited knowledge from previous cases to identify key concepts and management strategies that may be of benefit to the medical community.

Case overview: A four-month-old male was admitted to a New Zealand Hospital in status epilepticus. A history of inconsolable crying, subjective fevers and abnormal posturing was elicited. Examination found a spastic quadriplegic cerebral palsy. Investigation excluded infective causes. MRI and CT scans demonstrated atrophy of the cerebral cortex with calcification of the basal ganglia. CSF analysis showed elevated white cells and neopterin, and genetic analysis identified variants of unknown significance in the ADAR1 gene. A diagnosis of AGS was made. Treatment focused on managing complications including seizures, spasticity, and airway clearance.

Discussion overview: This case highlights AGS as a differential for TORCH syndrome. Complication management forms the basis of care. Current literature is limited, and future research is needed to understand the pathophysiology of the disease to develop treatments and management strategies.

Key Learning Points

1) Aicardi-Goutières Syndrome is a rare differential for TORCH Syndrome and should be considered when TORCH infections have been excluded.
2) Key clinical findings that help distinguish Aicardi-Goutières Syndrome from TORCH Syndrome include onset at four months, vasculitic lesions, absence of ocular anatomical pathology, and absence of hearing impairment.
3) Complication management currently forms the basis of care. A balance between treatments, side effects, and patient goals is required to achieve optimal outcomes for the patient.
4) The understanding of the genetic processes in Aicardi-Goutières Syndrome has allowed the investigation of future therapeutic agents such as JAK inhibitors, antiretrovirals, anti-IFN-alpha and cGAS inhibitors, and introduction of genetic counselling.

Introduction

Aicardi-Goutières Syndrome (AGS) is a rare genetic neurological condition first described in 1984 [1]. It is a Type 1 interferonopathy [2] and only 350 confirmed cases have been recorded worldwide by the International Aicardi-Goutières Syndrome Association [3]. Prior to its discovery, AGS was classified as pseudo-TORCH Syndrome due to the similar presentation to TORCH Syndrome in the absence of identifiable pathogens [4]. The disease typically begins in the fourth month of life with extreme irritability, disturbed sleep, feeding difficulties, and fever [5]. New research has enabled further understanding of the genetics and pathophysiology of AGS, contributing to the investigation of therapeutic agents and utilisation of genetic counselling [6, 7]. This study reports the hospital admission and diagnosis of a 22-month-old male with complications of Aicardi-Goutières Syndrome. A comprehensive history and retrospective analysis of patient notes was completed during this admission to obtain a clinical timeline of disease progression and the subsequent management from the initial presentation at the age of four months.

The Case

AA is a 22-month-old Caucasian male with a known diagnosis of AGS who was admitted to a New Zealand hospital. He was first diagnosed at four months of age after presenting to an emergency department with a generalised tonic-clonic seizure and status epilepticus. A detailed history on admission revealed daily episodes of inconsolable crying and the development of subjective febrile episodes. He had adopted an abnormal posture with extension of the upper limb, lower limb, and spine. Pregnancy and birth were uneventful with normal growth and development. The family conscientiously objected to vaccinations. An older half-brother (paternal) had a diagnosis of epilepsy. Examination demonstrated hypertonia in the upper limbs, lower limbs, and postural muscles consistent with a spastic quadriplegic cerebral palsy. Head circumference, weight, and height were measured on the 25^{th}, 50^{th}, and 50^{th} centiles respectively. The remainder of the examination was normal including the absence of hepatosplenomegaly. Blood tests showed elevated white cells and lymphocytes, with normal transaminases and platelets. The presence of seizures, extreme irritability, fevers, dystonia, and elevated white cells raised the possibility of an infective process involving the central nervous system. Therefore meningitis, encephalitis, and TORCH Syndrome were considered as possible causes in a patient of this age. However, after further investigation, both metabolic and infective causes including TORCH Syndrome and Human Immunodeficiency Virus (HIV) were excluded. It was decided computed tomography (CT) scan of the brain would be completed, which identified basal ganglia calcifications (Table 1). Subsequent magnetic resonance imaging (MRI) of the brain showed atrophy of the cerebral cortex with calcification of the basal ganglia and white matter (Table 1). Cerebrospinal fluid (CSF) analysis showed elevated white cells ($24x10^6$/L) and neopterin with the absence of infective aetiology. An electroencephalogram (EEG) was completed which was abnormal (Table 1). Genetic analysis identified two variants of unknown significance in the ADAR1 gene and a diagnosis of AGS was made. Management of seizures was initiated with levetiracetam, while spasticity was managed with clobazam and gabapentin.

At eight months of age he developed further symptomatology. He failed to meet further developmental milestones and exhibited developmental regression, thereby impacting on motor function, communication, and eye contact. Anatomical ocular pathology and hearing deficits were excluded. He had further generalised tonic-clonic seizures. Multiple admissions for respiratory tract illnesses complicated by an inability to clear airway secretions were attributed to disease progression and the use of benzodiazepines. A nasogastric tube was inserted for feeding and prevention of aspiration. Allied health input was sought for secretion clearance in conjunction with hyoscine patches. Levetiracetam and clobazam doses were increased to manage seizures and baclofen was added to improve dystonia.

At 12 months of age the care giver reported that there had been a reduction in seizure frequency. Examination showed a decline in head circumference, dropping to below the 3^{rd} centile. Height and weight remained consistent, being maintained at the 50^{th} centile. Further investigations showed that he had developed mild liver dysfunction with transaminitis.

At 22 months the caregiver reported that the abnormal posturing and spasticity had improved along with the frequency and severity of seizures. It was reported that he had begun to groan when having his hips moved and there was ongoing difficulty with the management of upper airway secretions. An X-ray of the pelvis showed bilateral hip dislocations which were managed conservatively. Given the reduction in seizure frequency, the dose of clobazam was reduced to assist in the reduction of airway secretions.

Discussion

Aicardi-Goutières Syndrome

AGS is an early onset encephalopathy resulting in severe intellectual and physical disability with symptoms including neurological impairment, seizures, acquired microcephaly, hepatosplenomegaly, abnormal liver function tests, and thrombocytopaenia [5]. Prior to its discovery, AGS was classified as pseudo-TORCH Syndrome due to its similar presentation with the absence of identifiable pathogens [4,8] (Table 2). Other differentials for AGS include mitochondrial cytopathies, Cockayne syndrome, organic acidurias, HIV, Zika virus, lupus erythematosus, microcephaly-intracranial calcification syndrome, and polymicrogyria [5,8,9]. There are two main subtypes of AGS, categorised as either early or late onset [10,11]. Late onset disease presents at the age of four months and is the most common presentation (80%), while early onset disease presents immediately after birth and comprises 20% of cases [10,11]. Disease progression is split into an initial acute phase of deterioration that lasts a few months, and a second long-term phase of disease stabilisation [5]. Life expectancy is variable with 25% of patients dying by the age of 17 years, with the remainder experiencing a considerable decrease in their quality of life [5,10].

A review of the literature by Orcesi *et al*. [5] highlighted that AGS typically begins in the fourth month of life with extreme irritability, disturbed sleep, feeding difficulties, and fever. The most common clinical features of the disease are mental impairment (92%), dystonia (75%), microcephaly (63%), seizures (50%), and chilblain lesions (42%) [12]. Clinical findings are similar between AGS and TORCH infections making it difficult to distinguish between them [5,13,14] (Table 2). In this case, the absence of anatomical ocular abnormalities suggested a central pathology [15]. This finding combined with the absence of hearing deficits made a diagnosis of TORCH Syndrome unlikely [5,13-15]. Although vasculitic lesions are common in AGS, they were not reported in this case [5].

Findings on investigation include a negative TORCH screen, basal ganglia calcification (50-70%), white matter abnormalities (75-100%), cerebral atrophy (94%), and CSF analysis showing lymphocytosis, elevated interferon alpha, and pterins [5]. Genetic abnormalities are identified in 83% of cases and include autosomal recessive (TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, ADAR) and autosomal dominant alleles (TREX, ADAR, IFIH1) [5,16]. In this case, the presence of both basal ganglia calcifications and ADAR1 variants were highly suggestive of AGS [16,17].

The current hypothesis is that a defect in the DNA damage response leads to an accumulation of endogenous DNA or DNA–RNA hybrids which trigger an interferon-alpha-mediated immune response similar to that which occurs during viral infections [5]. It is believed this malfunctioning of the interferon-alpha pathway is also responsible for the increased rate of autoimmune diseases in those with AGS [5].

Current treatments offer primarily symptomatic relief with the management of epilepsy, postural abnormalities, airway clearance techniques, and dietary intake comprising the primary long-term goals of treatment [11]. Screening for associated conditions including glaucoma, diabetes mellitus, and hypothyroidism should be considered [5]. Although no cure is currently available, corticosteroids may reduce the frequency of fevers and improve vasculitic skin lesions [7]. In addition, treatments targeting the interferon signalling pathways such as immune modulating therapies, JAK inhibitors, antiretrovirals, anti-IFN-alpha and cGAS inhibitors are emerging as possible therapeutic agents for interferonopathies [6, 7].

Management strategies

In the case presented it can be determined that AA had a late-onset form of AGS [18]. He exhibited a classical presentation of the disease with normal development followed by an acute phase of inconsolable crying, subjective febrile episodes, seizures, and dystonia [5,12]. This was then followed by a phase of disease stabilisation.

Access to new and novel medications for AGS in New Zealand is limited. The care in this case focused on managing complications of the disease rather than treating the disease itself and, as such, general paediatric guidelines from the New Zealand Starship Hospital were followed [19]. Seizures were managed according to generalised epilepsy guidelines with levetiracetam and clobazam, while spasticity was managed with baclofen and gabapentin as per cerebral palsy guidelines [19]. Clobazam, however, had the undesired effect of increasing oral secretions. Feeding and airway secretions were managed by allied health professionals to prevent malnourishment and reduce the risk of aspiration [19]. Hip dislocation in AGS is not well documented in the literature. Research suggests patients with spasticity are at risk of hip dysplasia due to abnormal force loading through the joints [20]. Surgical correction is an option for pain and impaired mobility [20], however after discussion with the family and an orthopaedic consultation, it was decided that surgical intervention would be unwarranted given the degree of functional impairment. This case highlights the balance between treatments, side effects, and patient goals to achieve optimal patient care.

Future considerations

Although a rare disorder, AGS should be considered in patients who present with the signs and symptoms of TORCH Syndrome in the absence of an identifiable pathogen [11]. The disease follows a distinct clinical progression and as such may be identifiable by the informed clinician allowing timely introduction of therapies used for interferonopathies. Key distinguishing factors include onset at four months of age, vasculitic lesions, absence of hearing deficits, absence of ocular anatomical pathology, acquired microcephaly in the first year of life, and a negative TORCH screen [5,13-15]. The rarity of the condition dictates that large-scale quality research papers are not feasible, therefore small cohort studies form the core of current research. Nevertheless, it is promising that novel treatments such as immune modulating therapies, JAK inhibitors, antiretrovirals, anti-IFN-alpha and cGAS inhibitors may be able to treat the disease itself [6,7]. Future research should focus on developing understanding of the pathophysiology, treatments for the disease, and management of disease complications.

Consent Declaration

Informed consent was obtained from the patient's family for publication of this case report and accompanying figures.

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Conflicts of Interest

None.

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None.

Author Contributions

Sole author.

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