

## CASE REPORT

# Endocrinopathies in Aicardi Goutières syndrome—A descriptive case series

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## Abstract

Hypothyroidism and diabetes insipidus present in children with Aicardi Goutières Syndrome (AGS) often years after disease onset and frequently resolve spontaneously. Screening and regular reassessment for both conditions are recommended in all children with AGS.

## KEYWORDS

adolescent medicine, endocrinology and metabolic disorders, genetics, pediatrics

## 1 | INTRODUCTION

Aicardi Goutières Syndrome (AGS) is a rare genetic condition which often presents in the neonatal period with abnormal neurology, thrombocytopenia, hepatosplenomegaly, intracranial calcification, and white matter disease, reminiscent of a congenital TORCH infection but without serological evidence. Some patients, however, present later in infancy with encephalopathy, irritability, sterile pyrexias and developmental regression or delay.<sup>1</sup> There are seven genes described as causative of AGS: *TREX1*, *RNASEH2A*, *RNASEH2B* or *RNASEH2C*, *SAMHD1*, *ADARI*, and *IFIH1* all of which have

an integral role in nucleic acid sensing/metabolism. Patients with AGS have elevated levels of type I interferon and interferon-stimulated genes (ISGs)<sup>2,3</sup>.

Endocrinopathies in AGS are recognized but not well clinically described. In a series of 374 patients with AGS, hypothyroidism was documented in 14 patients and diabetes insipidus (DI) in four patients<sup>3</sup> but full clinical details of endocrine manifestations are not available. We provide a detailed description of endocrinopathies in five patients with AGS, all of whom had deranged thyroid function, with DI presenting in two of the five. We provide a discussion of the possible pathogenesis of hypothyroidism in AGS and

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recommendations for the care of these patients from an endocrine perspective.

## 2 | CASE REPORTS

### 2.1 | Patient 1

Patient 1 was noted to have intracranial calcification following CT scan during the neonatal period. Congenital infection with cytomegalovirus (CMV) was ruled out via PCR test. AGS was confirmed at 12 months of age with the identification of a homozygous splice site pathogenic *SAMHD1* variant (Table 1). The patient was referred to the endocrinology team at 27 months of age due to a raised thyroid-stimulating hormone (TSH) and normal free thyroxine (fT4) (Table 1) but no clinical features of hypothyroidism, consistent with a diagnosis of subclinical hypothyroidism (SCH). Free triiodothyronine (fT3) was normal, and thyroid peroxidase antibodies (TPO abs) were not measured (Table 1). The patient was not commenced on levothyroxine and thyroid function tests (TFTs) remained unchanged for several years (Table 1) until the patient died aged 4 years and 10 months secondary to chronic lung disease and sepsis.

### 2.2 | Patient 2

Patient 2 presented in the neonatal period with microcephaly and respiratory failure requiring ventilation. Intracranial calcification was detected on ultrasound scan and confirmed on MRI scan. CT was not performed. An infection screen for Toxoplasmosis, Rubella, CMV, Herpes simplex, and HIV (TORCH screen) was negative. Diagnosis of AGS was confirmed at 4 months of age with demonstration of compound heterozygous *TREX1* pathogenic variants (Table 1).

Hypernatremia was detected in the first few days of life with paired serum (300 mmol/kg) and urine (77 mmol/kg) osmolalities confirming the diagnosis of diabetes insipidus (DI). The patient was commenced on desmopressin, the dose of which varied from 5 mcg BD to 5 mcg TDS according to clinical symptoms. At 13 months of age, desmopressin was discontinued and the patient remained normonatremic and normovolemic for the following 2 years until they died aged 3 years secondary to unrelated causes.

Initial TFTs performed at 1 month of age were normal with a TSH of 3.1 mU/L and fT4 of 23.4 pmol/L. At 5 months of age, TSH was raised but fT4 remained in the normal range (Table 1). No clinical features of hypothyroidism were present, consistent with a diagnosis of SCH. fT3 was normal, and thyroid peroxidase antibodies (TPO abs) were not measured (Table 1). The patient was not commenced on levothyroxine

and thyroid function tests (TFTs) remained unchanged for several years (Table 1) until the patient died aged 3 years.

### 2.3 | Patient 3

Patient 3 presented at eight days of age with thrombocytopenia and recurrent apneas. They were found to be hypernatremic and polyuric and started on 3 mcg twice a day (BD) of desmopressin to treat DI. Desmopressin was discontinued prior to discharge from hospital. TORCH screen was not supportive of congenital infection, and genetic diagnosis of AGS was confirmed at 3 months of age with demonstration of compound heterozygous pathogenic *TREX1* variants (Table 1). An elevated ISG was observed, in keeping with the diagnosis.

At 2 months of age, desmopressin was recommenced at 4 mcg BD to treat hypernatremia and polyuria. Doses were adjusted according to urine output and serum sodium until, aged 5 years, the patient was trialed off treatment due to a modest dose requirement of 5 mcg morning/6 mcg evening. Serum sodium and urine output remained stable for 12 months until the patient died aged 6 years secondary to complications from bowel perforation.

Initial TFTs showed a mildly raised TSH of 6.1 mU/L and a fT4 of 17.0. TSH remained high, and subsequently, the patient was commenced on 25 mcg of levothyroxine at 2 months of age which suppressed TSH (Table 1). TPO abs were negative (<33 kU/L), and an ultrasound scan of the thyroid gland was normal. No clinical features of hypothyroidism were present, consistent with a diagnosis of subclinical hypothyroidism (SCH). Aged 5 years, levothyroxine was discontinued and TFTs remained normal until the patient died aged 6 years (Table 1).

### 2.4 | Patient 4

Patient 4 presented at 5 months of age with possible seizures and significant developmental delay. MRI scan demonstrated diffuse cerebral atrophy with severely delayed white matter myelination. At 23 months of age, intracranial calcification was demonstrated on CT imaging, and AGS was confirmed via detection of homozygous *RNASEH2C* pathogenic variants at 27 months of age (Table 1).

TFTs at 10 months of age were normal and were not repeated until 6 years of age when TSH was found to be mildly raised at 11.8 mU/L and fT4 normal at 13.6 pmol/L. Levothyroxine 25 mcg was commenced and suppressed TSH to 0.1 mU/L and raised fT4 to 26.6 pmol/L. Subsequent doses varied between 12.5 mcg and 25 mcg OD (Table 1). TPO abs were positive at 81 kU/L (reference <59 kU/L), and thyroid ultrasound showed a slightly small thyroid with ill-defined

**TABLE 1** Demographics and clinical markers of all five patients

Patient	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5										
Gene (Mutation)	<i>SAMHD1</i> c.1609-1G>C Hom	<i>TREX1</i> c.58dupG (p.Glu20fs) het; c.212_213dupTG (p.Ala72fs) het	<i>TREX1</i> c.58dup (p.Glu20Glyfs*82) het; c.625_628dup (p.Trp210Serfs*32) het	<i>RNASEH2C</i> c.205C>T (p.Arg69Trp) Hom	<i>TREX1</i> c.243_246del (p.Ser82Argfs*5) het; c.341G>A (p.Arg114His) het										
Interferon-stimulated gene signature	No data	No data	Elevated on 4 separate occasions	No data	Elevated on 4 separate occasions										
Diabetes Insipidus?	No	Yes	Yes	No	No										
TPO ab status	Not done	Not done	<33 KU/L	81 KU/L	<33 KU/L										
Thyroid USS	Not done	Not done	Normal	Small, echogenic	Normal										
Intracranial calcifications?	On CT	On MRI	No scan performed	On CT	On MRI										
	<b>TSH</b>	<b>FT4</b>	<b>FT3</b>	<b>TSH</b>	<b>FT4</b>	<b>FT3</b>	<b>TSH</b>	<b>FT4</b>	<b>FT3</b>	<b>TSH</b>	<b>FT4</b>	<b>FT3</b>	<b>LT4 dose</b>	<b>FT4</b>	<b>LT4 dose</b>
Initial	14.5	21.7	3.1	3.1	23.4	23.4	6.1	17.0	4.0	20.3	20.3	25 mcg	6.7	19.3	19.3
At initiation of treatment	–	–	–	–	–	–	12.4	16.6	11.8	13.9	13.9	25 mcg	9.7	15.2	25 mcg
On treatment	–	–	–	–	–	–	0.09	19.8	0.1	26.6	26.6	12.5 mcg	7.3	19.3	19.3
Midpoint	15.3	22.0	6.9	17.6	18.7	18.7	3.8	19.8	Stopped	Stopped	Stopped	Stopped	6.2	19.4	19.4
Last	10.9	19.3	12.7	12.7	22.8	22.8	3.1	15.4	9.8	18.3	18.3	25 mcg	4.0	16.4	16.4
	Died aged 4 y	Died aged 4 y	Died aged 3 y	Died aged 3 y	Died aged 3 y	Died aged 3 y	Died aged 6 y	Died aged 6 y	Died aged 2 y	Died aged 2 y	Died aged 2 y	Died aged 2 y	Died aged 2 y	Died aged 2 y	Died aged 2 y

Note: Clinical data are provided regarding genetics, thyroid scan, diabetes insipidus, TPO ab, and interferon status. Thyroid function results are reported from key points in the patients' treatment journeys.

Abbreviations: CT, computed tomography scan; FT3, triiodothyronine (pmol/L, Normal range 3.0-6.9); FT4, free thyroxine (pmol/L, Normal range 11-24 pmol/L); LT4, levothyroxine; MRI, magnetic resonance imaging; TPO ab, thyroid peroxidase antibody (KU/L, Normal range <59 KU/L); TSH, thyroid-stimulating hormone (mU/L, Normal range 0.3-5.0 mU/L); USS, ultrasound scan.

increased echogenicity in both lobes indicating possible thyroiditis. No clinical features of hypothyroidism were present, consistent with a diagnosis of subclinical hypothyroidism (SCH).

## 2.5 | Patient 5

Patient 5 presented with abnormal movements soon after birth. MRI demonstrated intracranial calcifications, and TORCH screen was not suggestive of congenital infection. Diagnosis of AGS was confirmed at 5 months of age via detection of homozygous *TREX1* pathogenic variants and elevated ISGs (Table 1).

Initial TFTs at 8 months of age demonstrated a mildly raised TSH of 6.7 mU/L with subsequent normalization to 3.0 mU/L after 3 months. Between 15 and 19 months of age TSH was persistently raised with a normal fT4 (Table 1). The patient was treated with levothyroxine 25 mcg until aged 2 years 11 months when the patient died secondary to cardiac failure. TPO abs were negative (<33 kU/L), and ultrasound scan of the thyroid gland was normal. No clinical features of hypothyroidism were present, consistent with a diagnosis of subclinical hypothyroidism (SCH).

## 3 | DISCUSSION

The pathology of hypothyroidism in AGS is not understood. Thyroid dysfunction in these patients fits the criteria for SCH<sup>4</sup> and is suggestive of primary disease with raised TSH, normal fT4, and suppression of TSH with levothyroxine.

The most common cause of SCH is an autoimmune thyroiditis<sup>5</sup> secondary to lymphocytic infiltration and the production of autoantibodies directed against TPO, thyroglobulin, or TSH receptors.<sup>5</sup> This inflammation generates cytokines which can induce either hypothyroid illness or nonthyroid illness biochemical changes.<sup>6</sup> AGS triggers a type I interferon-mediated autoimmune response<sup>7</sup> characterized by elevated ISGs,<sup>8</sup> and this may result in antibodies directed against the thyroid and autoimmune disease. However, very few patients with AGS demonstrate abnormal autoantibody profiles.<sup>8</sup> This may be due to immunoassay insensitivity, as up to 40% of patients with autoimmune thyroid disease have negative TPO ab when analyzed with an ImmunoCAP assay on a Phadia 250 Immunoassay Analyser. Nonetheless, thyroid disease in AGS may be nonimmune mediated as interferon can cause thyroiditis via direct toxic effects<sup>9</sup> as well as via disruption of immune tolerance. Receiving exogenous interferon therapy causes autoimmune and nonautoimmune thyroiditis<sup>9,10</sup> so the high levels in patients with AGS may cause thyroid disease

via a nonimmunological pathway through direct toxic effect. As is the case for most patients, both patients in our series who had ISGs measured demonstrated elevated levels (and negative TPO abs).

None of our patients were symptomatic of thyroid disease. Most presented after an initially normal set of TFTs so would have been missed without regular screening of thyroid function every 6 months. International guidelines recommend that SCH is treated with levothyroxine when TSH exceeds 10 mU/L<sup>5</sup> (independent of symptoms) and this should be withdrawn when no longer required. Given the delayed, clinically asymptomatic presentation of SCH in AGS patients and current international guidance on the management of SCH, we recommend low dose levothyroxine for patients with AGS when TSH values exceed 10 mU/L. Also, in view of the transient nature of TSH elevation in some, we would recommend monitoring of thyroid function 6 monthly. In patients requiring treatment who are above the age of 2 years, if thyroid function results remain normal without the need for treatment dose escalation, we recommend a trial of withdrawal of treatment after 12–18 months of treatment to determine whether thyroid treatment is still required. Our recommendation for regular screening will ensure appropriate treatment of SCH at an early stage in young patients with AGS and ensure cessation of that treatment when no longer required.

In those requiring treatment with Desmopressin, both patients required less than 10% of the recommended dose for age of Desmopressin as per the Children's British National Formulary. Both patients were also successfully trialed off treatment and remained normovolemic and normonatremic. We recommend regular testing of patients with AGS for DI and if started on treatment a regular assessment to see whether treatment can be discontinued.

## 4 | CONCLUSION

In this series of five patients with AGS, we have described the derangement in thyroid and antidiuretic hormone (ADH) function, endocrine treatment, and longer-term outcomes. We have described the difficulty in reliance upon clinical signs to detect endocrinopathies in these patients and therefore the requirement for regular screening. We recommend yearly screening for hypothyroidism in AGS patients with yearly retesting due to the observed transient nature. We also recommend serum sodium measurement for screening patients with AGS for DI and starting modest doses of DDAVP if indicated, as this makes a positive difference to fluid and electrolyte imbalance. Regular re-assessments are advised due to the transient nature of DI.

## 5 | RECOMMENDATIONS

Testing of serum electrolytes in first week of life to screen for evidence of diabetes insipidus (DI).

If DDAVP required to treat DI, start with a low dose.

Regular reassessment of serum electrolytes in those with DI with a low threshold to trial off treatment.

Thyroid function tests (TFTs) to screen for hypothyroidism every 6 mo.

Yearly retesting of TFTs in those with hypothyroidism to assess for permanence of disease.

### CONFLICT OF INTEREST

We report no conflict of interest.

### AUTHOR CONTRIBUTION

CW: collated patient information and wrote the initial manuscript, he viewed and approved the final version. TB was genetic lead for the patients and provided genetic information for the manuscript and viewed and approved the final version. RP, EB, and MS: provided consultant level care for the patients, were involved in drafting the manuscript, and viewed and approved the final manuscript. All authors: meet the Author Guidelines criteria for authorship.

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