

# THE NEUROPATHOLOGY OF AICARDI-GOUTIÈRES SYNDROME - A REVIEW

Peter G. Barth, M.D.

Correspondence: Prof. Peter G. Barth,  
Department of Pediatric Neurology, Emma Children's Hospital/ AMC, University of  
Amsterdam

Address: P.O. box 22700 1100DE Amsterdam - The Netherlands

Category: Review

Running head: *AGS Neuropathology*

## **Summary**

Aicardi-Goutières syndrome (AGS) is an autosomal recessive neurodegenerative disorder with unique characteristics which include CSF lymphocytosis, cytokine involvement (interferon alpha in plasma and in CSF), a unique distribution of cerebral calcifications, and early loss of myelin. Surprisingly only a very small number of detailed neuropathological studies are available. This paper summarizes the findings. Calcifications are both present as concretions and as perivascular cuffs of calcium surrounding small vessels. Small vessel involvement (microangiopathy) is apparent from a typical distribution of microinfarctions in at least one case studied. Together with signs of extracerebral vascular involvement known from earlier reports this finding points to microangiopathy as an important pathogenic mechanism in AGS.

Key words: Aicardi-Goutières syndrome - microangiopathy - cerebral calcification

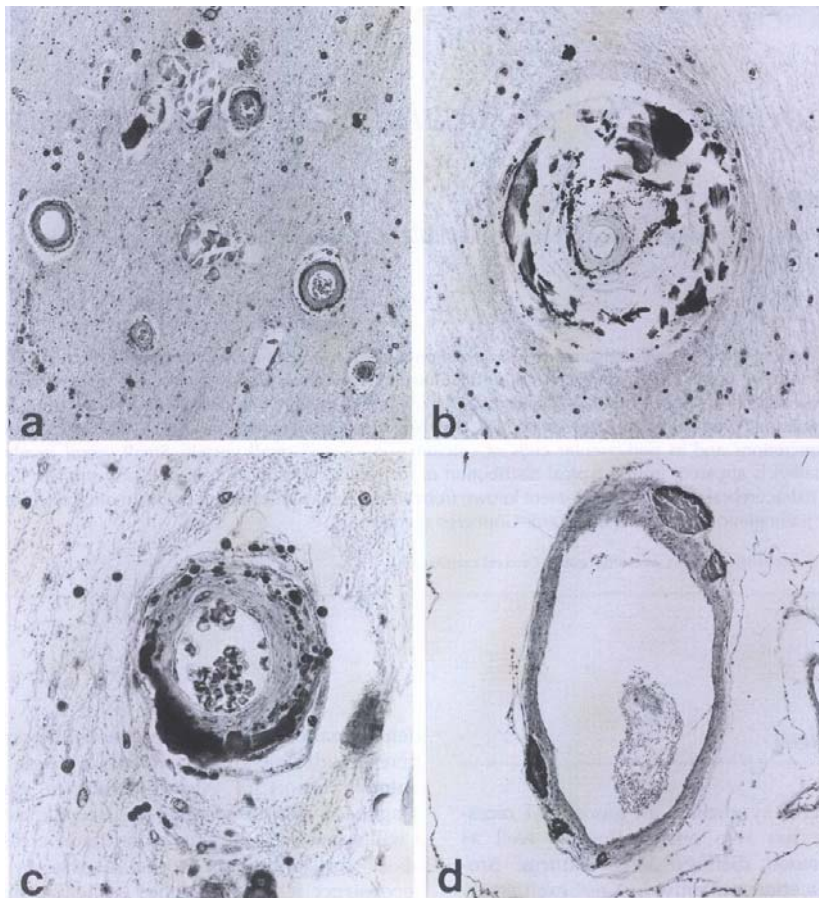
## ***Introduction***

Aicardi-Goutières syndrome (AGS), an autosomal recessive disorder, has two outstanding as well as poorly understood distinguishing features: progressive calcifications, mainly, but not exclusively in the basal ganglia and a low-level chronic lymphocytic pleiocytosis in the CSF.

The now classic paper by Jean Aicardi and Françoise Goutières in 1984<sup>1</sup> was based on clinical examination and CSF studies while neuroimages were acquired by way of CT-scanning. Earlier studies that in retrospect might have been AGS cases were cited, including autopsy findings, but these studies did not mention CSF cytological findings. As a consequence uncertainty remained whether these earlier studies referred to patients with “AGS *avant la lettre*”. Another crucial finding was only emphasized in later studies after the emergence of MRI as an imaging tool: the severe demyelination which accompanies AGS. Until now only a single detailed autopsy report of AGS, diagnosed during lifetime has become available<sup>2</sup>. I will summarize this report and add a discussion about the pathology of the disease as we can reconstruct it from possible earlier AGS cases, and related disorders which - in retrospect- may have been AGS.

### ***Neuropathological findings***

The patient on which this review centres became 17 years old and had a diagnosis of AGS made during his life based on a characteristic CT-scan, a similarly affected sister and the presence of CSF lymphocytosis. Details of the neuropathological findings have been published previously<sup>2</sup>.

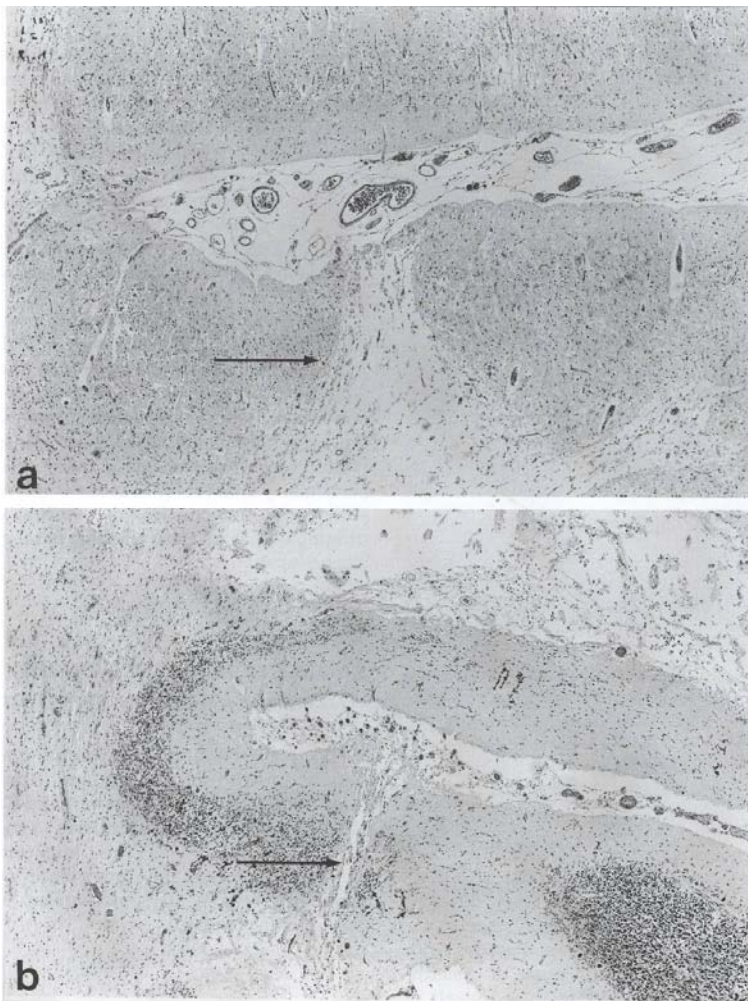


The main findings can be summarized as follows:

1. Severe microencephaly,

2. Diffuse but characteristically inhomogeneous demyelination with associated astrocytosis and absence of signs of storage or overt signs of myelin breakdown,
3. Calcific deposits in the white matter, thalami, basal ganglia and dentate nuclei,
4. Involvement of the neocortex and the cerebellar cortex by a multitude of wedge-shaped micro-infarctions,
5. Small vessel calcification in the media, adventitia and perivascular spaces,
6. Inflammation, limited to areas of necrosis and the leptomeninges.

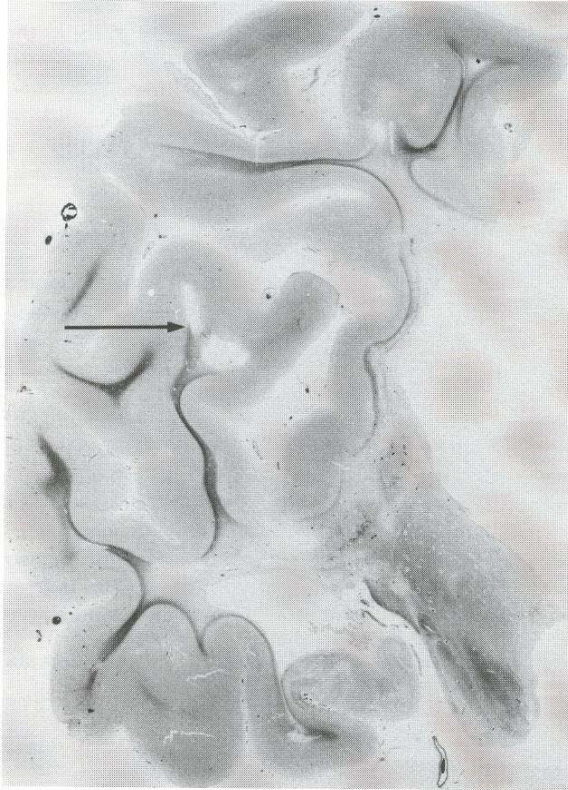
The manifold abnormalities encountered in transverse sections of vessels can be seen in Figure 1. Shown are calcifications in small veins and arteries. Most abnormal vessel profiles are arterioles. The calcified masses are seen in the thickened media, the adventitia and the periadventitial spaces. Overt thrombosis is not seen in any place. However, in view of the very abnormal shape of the affected vessels, it is highly likely that their contractile properties were affected, and that this pathology was the cause of the wedged shaped micro-infarctions encountered in many areas of the cerebral and cerebellar cortex.



Demyelination was found, both in the cerebral hemispheres, and in the brainstem and the cerebellum (Figure 2), without presence of lipid laden macrophages. It is not possible to tell whether the demyelination was solely related to the vascular abnormalities. The irregular distribution of the demyelination and its variable intensity over short distances (Figure 3) certainly suggests that vascular impairment may have had some influence on the loss of myelin.

### *Related neuropathological and experimental studies*

Cerebral microangiopathies in the context of a genetic disorder are distinctly rare. Two examples, otherwise completely different from AGS are CADASIL<sup>3</sup> and Cerebro-Oculo-Facio-Skeletal syndrome (COFS)<sup>4</sup>. Both these diseases are otherwise very different from AGS. Kumar et al.<sup>5</sup> described an autosomal recessive disorder with features that were very reminiscent of AGS including increased levels of interferon alpha in two cases examined.



Autopsy in two cases revealed diffuse cerebral atrophy, and extensive cerebral calcification mostly seen as calcified areas within the white matter and basal ganglia, but occasionally around and within vessel walls. Extensive loss of white matter was noted. In 1988, “encephalitis” in children belonging to the Cree Indians in Northern Quebec was reported<sup>6</sup>. This report on a disease which is probably identical to Aicardi-Goutières syndrome includes four cerebral autopsies. The findings were summarized as: “chronic panmeningoencephalitis with numerous calcifications and severe vascular changes primarily involving the white matter”, implicitly stating that the loss of white matter may have had a vascular origin.

A recent update on Aicardi-Goutières syndrome by the original authors<sup>7</sup> includes two brief autopsy reports. One is a summary of the present report, the other, shows a similar affection with foci of necrosis and vascular calcifications. Earlier reports that may have been cases of AGS includes a case described by Melchior et al.<sup>8</sup> Their case 4 is particularly well illustrated and conforms in most aspects to the present report and two sibs with an identical disease reminiscent of the former one<sup>9</sup>.

The high levels of interferon alpha (IFN), found in CSF and serum, especially in younger children with AGS raises the question whether this cytokine represents an epiphenomenon or a pathogenic element in its own strength. In this regard the neuropathology of transgenic mice with cerebral expression of IFN<sup>10</sup> is particularly interesting because it includes angiopathy with mononuclear cell cuffing as well as progressive calcification affecting basal ganglia and cerebellum.

## ***Extracerebral vasculopathy and Aicardi-Goutières syndrome***

“Chilblains”, presenting as painful, cyanotic acra, sometimes with ulcerations and resulting from distal small vessel involvement were described in patients with AGS by various authors <sup>6,7,11,12</sup>. This important finding similarly indicates the importance of vascular involvement as a pathomechanism in AGS.

### ***Consequences for further investigations***

More and detailed descriptions of the neuropathology of AGS are needed to underscore the present findings. However, the facts that surfaced so far also bear on the way in which the disease can be approached by MRI and MRS techniques. The possibility that necrosis, calcification and even demyelination could be caused by cytokine related vasculopathy invites some new thinking about approaches to therapy in this devastating disease.

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### ***Legends to Figures***

Fig. 1. Central cerebellar white matter. H&E stain.

- a. Low magnification showing a number of transverse sectioned small vessels with surrounding dark calcifications. Small black dots represent solitary calcifications outside blood vessels.
- b. Transverse section of arteriole with calcifications in adventitia and perivascular space.
- c. Transverse section of arteriole with thickened media containing massive calcifications.
- d. Transverse section of thin walled vessel and calcific masses.

Fig. 2.

- a. Cerebral cortex with wedge shaped area of infarction (arrows). An other infarction can be seen on the left side. The leptomenigeal vessels are increased in number (H&E stain).
- b. Cerebellar cortex with wedge shaped infarction (arrows) (H&E stain).

Fig. 3.

Transverse section of the brain at the level of the thalamus. (Luxol fast blue stain for myelin). Gross gyral atrophy. Demyelination with relative sparing of the subcortical white matter. Small cavitated regions (arrow) illustrates inhomogenous demyelination.