Aicardi-Goutières syndrome – observations of the Glasgow school

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Thank you for the opportunity to speak and thanks to the audience for still being here. I am going to be talking fairly personally about Scotland and in part about a family who are in the room at this meeting. I am just going to emphasize in a few minutes some observations of the Glasgow school.

Clinico-pathological discordance.
By clinico-pathological discordance I mean that, although the pathology is commonly progressive, with increasing calcification on brain CT scan, actually the children we have seen with AGS don’t necessarily seem to their parents or even to their doctors to get worse at all. Figure 1a shows an affected singleton girl (whom the Society doesn’t yet know about) at the age of 10 months, not yet smiling, and demonstrating a strange movement disorder. Figure 1b shows her again when she was 7 years old, smiling and laughing. She did not laugh till she was 3 years’ old, and her mother did not recognise any regression. However, she did develop the so-called chilblain lesions on the toes as discussed below.

Pseudo-TORCH equivalence
The identity of pseudo-TORCH (microcephaly intracranial calcification syndrome) and AGS has been noted by us\textsuperscript{1,2} but this has been discussed, and I think we agreed about that already.
Intra-familial variability

Figure 2a – taken from the video – shows a little girl whose parents are here, aged about 4 months. If she had been a singleton, without a sibling with known AGS, I think it would have been very difficult for anyone to diagnose her, because she has not regressed, she is relatively mildly affected, her neurological phenotype has been of athetoid cerebral palsy (resembling case 2 [IV 5] of McEntagart et al4), she makes developmental advances constantly, her initial CT was normal, and her MRI was normal. Figure 2b shows her elder brother, who is very much more severely affected when aged 3 years (he is now 12). His CT images showing white matter loss and gross calcification involving basal ganglia, white matter and dentate nuclei have previously been published3. The diagnosis of AGS was confirmed after I took his specimens personally, in an airplane, to professor Pierre Lebon for alpha-interferon assay. These siblings demonstrate that great intrafamilial variability is possible.

Chilblains

John Tolmie, Paul Shillito and I cared for two unrelated children with AGS who had severe chilblains (Figures 1b, 2b) despite their living in warm houses. We therefore
reported this as a feature of AGS in 1995. Chilblains as we have heard are not rare. The boy in Figure 2b had very startling chilblains on the toes and to a lesser extent on the hands and the ears. Figure 3a is a close-up of his toes. Although they look like vasculitis, you don’t see it on biopsy; you see what looks like lupus erythematosus with IgM granular staining in the basement membrane (Figure 3b). I would say that this chilblain lupus is as diagnostic for AGS as interferon alpha increase without viral infection or tubuloreticular inclusions.

**Magnetic resonance spectroscopy**

Finally, I will show you the proton MRS of the little girl (Figure 2a) who had a normal CT age 2 months and a normal MRI (Figure 4a) at the age of 5 months. In the $^1$H MRS performed at the same time, her spectra (Figure 4b) showed reduced NAA and increased lactate. The details will be reported elsewhere, but I think that $^1$HMRS is probably a sensitive way to look at patients with suspect AGS if you have the technology to do it at the same time as MRI. Later on this girl had a little bit of calcification on CT, but not much.

That’s all, thank you for your attention.

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**References**

Legends for Figures

Figure 1  [a] 10 month girl with movement disorder
   [b] same girl age 7 years laughing; chilblains on feet not shown

Figure 2  [a] relatively mildly affected younger sister of boy in Figure 2b
   [b] severely affected first born brother; chilblains on toes

Figure 3  [a] toes of boy in Figure 2b showing severe chilblain lupus
   [b] direct immunofluorescence of skin biopsy shows finely granular
       staining of the basement membrane zone for IgM only

Figure 4  [a] MRI of girl in Figure 2b age 5 months, normal for age
   [b] one of the spectra from $^1$H MRS done at the same examination

Please note: the order of colour figures on the Zip disc is:
1. fig. 4a
2. fig. 3a
3. fig. 3b
4. fig. 2a
5. fig. 2b
6. fig. 1b
7. fig. 4b
8. fig. 1a