Neuroradiologic patterns and novel imaging findings in Aicardi-Goutières syndrome

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ABSTRACT

Objective: To perform an updated characterization of the neuroradiologic features of Aicardi-Goutières syndrome (AGS).

Methods: The neuroradiologic data of 121 subjects with AGS were collected. The CT and MRI data were analyzed with a systematic approach. Moreover, we evaluated if an association exists between the neuroradiologic findings, clinical features, and genotype.

Results: Brain calcifications were present in 110 subjects (90.9%). Severe calcification was associated with *TREX1* mutations and early age at onset. Cerebral atrophy was documented in 111 subjects (91.8%). Leukoencephalopathy was present in 120 children (99.2%), with 3 main patterns: frontotemporal, diffuse, and periventricular. White matter rarefaction was found in 54 subjects (50.0%), strongly associated with mutations in *TREX1* and an early age at onset. Other novel radiologic features were identified: deep white matter cysts, associated with *TREX1* mutations, and delayed myelination, associated with *RNASEH2B* mutations and early age at onset.

Conclusions: We demonstrate that the AGS neuroradiologic phenotype is expanding by adding new patterns and findings to the classic criteria. The heterogeneity of neuroradiologic patterns is partly explained by the timing of the disease onset and reflects the complexity of the pathogenic mechanisms. ***Neurology*® 2016;86:28–35**

GLOSSARY

AGS = Aicardi-Goutières syndrome; **GRE** = gradient-echo imaging; **SWI** = susceptibility-weighted imaging.

Aicardi-Goutières syndrome (AGS) is a genetic immune-mediated disorder caused by mutations in one of 7 genes (*TREX1*, *RNASEH2B*, *RNASEH2C*, *RNASEH2A*, *SAMHD1*, *ADAR1*, and *IFIH1*) identified to date.[1–5]

Brain calcification, leukoencephalopathy, and cerebral atrophy are the classic hallmarks of the disease and have suggested the diagnosis of AGS in the majority of cases.[6–8] A phenotype reminiscent of the sequelae of congenital infection hinted at a role for an immune and inflammatory response in the pathogenesis of AGS. This possibility was confirmed by the discovery that the causal genes for AGS are involved in nucleic acid metabolism or signaling, which, when mutated, can trigger a reaction similar to that in response to a viral infection.[9] The characterization of neuroradiologic features has, therefore, been helpful in providing insights into the underlying pathogenesis of AGS.

Enhanced awareness of the disease in recent years has led to an increased number of diagnosed patients.[10] However, the disease is likely underdiagnosed, in part because of a lack of recognition by clinicians, but also possibly due to clinical[9,11–15] and radiologic[16–24] variability.

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Thus, a more detailed and updated characterization of the neuroradiologic features is needed.

The aim of our study is to provide an overview of the neuroradiologic findings in a large sample of patients with AGS. Our study has 3 specific objectives: to (1) review and update the classical neuroradiologic criteria; (2) characterize the MRI patterns of white matter involvement; and (3) investigate the presence of associations between neuroradiologic findings and genetic and clinical data.

METHODS

Population. We collected the neuroradiologic imaging data of 121 subjects with AGS. Patients were recruited in referral centers for AGS (Manchester, Pavia, Leeds, and Washington, DC) through the European Project FP7 (nuclease immune-mediated brain and lupus-like conditions). Clinical data were available through a shared database (REDCap[25]).

The diagnosis of AGS was made if mutations in one of the 7 genes known to cause AGS were identified in the context of a neurologic phenotype or if the previously established clinical and laboratory criteria for a diagnosis of AGS were met.[11,17] Most patients with genetic diagnosis conformed to the clinical diagnosis of AGS already defined. Some patients had supporting data in the form of an interferon signature.[26]

The severity of the clinical picture was assessed by deriving a score formed by addition of the scores obtained using 3 evaluation scales—Gross Motor Function Classification System, the Manual Ability Classification System, and the Communication Function Classification System. The total score ranges from 3, when gross motor, manual, and communication abilities are fully preserved, to 15, associated with very severe disability.

Standard protocol approvals, registrations, and patient consents. The institutional review boards of each participating institution approved the use of clinical data for the study.

MRI and CT and systematic analysis. The analysis of neuroradiologic images included evaluation of the 3 classic neuroradiologic criteria and specifically the pattern of white matter involvement. All images were reviewed by the authors (R.L.P., C.U., I.O., D.T., J.L., S.O.) using a standardized scoring approach for the assessment of calcification,[17]leukoencephalopathy, and atrophy,[16] as detailed in table e-1 on the *Neurology*® Web site at Neurology.org. The presence, localization, and severity of brain calcification were estimated using head CT images. In some patients for whom CT images were not available, calcification was often demonstrable on MRI as areas of high signal on T1-weighted or low signal on T2-weighted images, gradient-echo imaging (GRE), or susceptibility-weighted imaging (SWI). Severe calcifications were defined as involving multiple locations beyond the classical ones—lentiform nuclei, deep white matter, thalami—and having multiple and variable patterns, as previously described.[27]

Magnetic resonance images were reviewed to evaluate the presence, localization, and severity of cerebral atrophy and leukoencephalopathy, as specified in table e-1.

Association among neuroradiologic, clinical, and genetic data. We evaluated if an association exists among neuroradiologic findings, clinical features data, and genotype. The associations tested were selected based on previous findings[16] and possible pathophysiologic explanation (i.e., inadequate myelination and age at onset). Several models of logistic regression analysis were used to test the association. Neuroradiologic features (frontotemporal white matter rarefaction, cysts outside the frontotemporal regions, presence of severe calcifications, progressive calcifications, delayed myelination, anteroposterior pattern, diffuse pattern, periventricular pattern) were considered dependent variables. Independent variables were the genotype and clinical findings (age at onset, total score of clinical assessment). Age at onset was transformed into a dichotomous variable ($\leq$3 months, corresponding to early onset, vs $>$3 months) to increase power, while clinical assessment was tested both as a dichotomous variable ($<$12 vs $\geq$12, corresponding to severe disability) and as a continuous variable. Age at onset and total score of clinical assessment were tested both unadjusted and adjusted for mutated genes to avoid bias. Stata v11.2 software was used to perform statistical analysis.

RESULTS

Images from 121 patients (70 male) were reviewed. The mean age at first MRI examination was 22.6 months (range 1 week–19 years).

AGS causing mutations was present in 114 patients as follows: *RNASEH2B* in 51 subjects, *TREX1* in 24, *RNASEH2C* in 9, *RNASEH2A* in 8, *SAMHD1* in 12, *ADAR1* in 8, and *IFIH1* in 2. In 7 cases, no mutations were found, but these patients fulfilled clinical and biochemical criteria for a diagnosis of AGS.

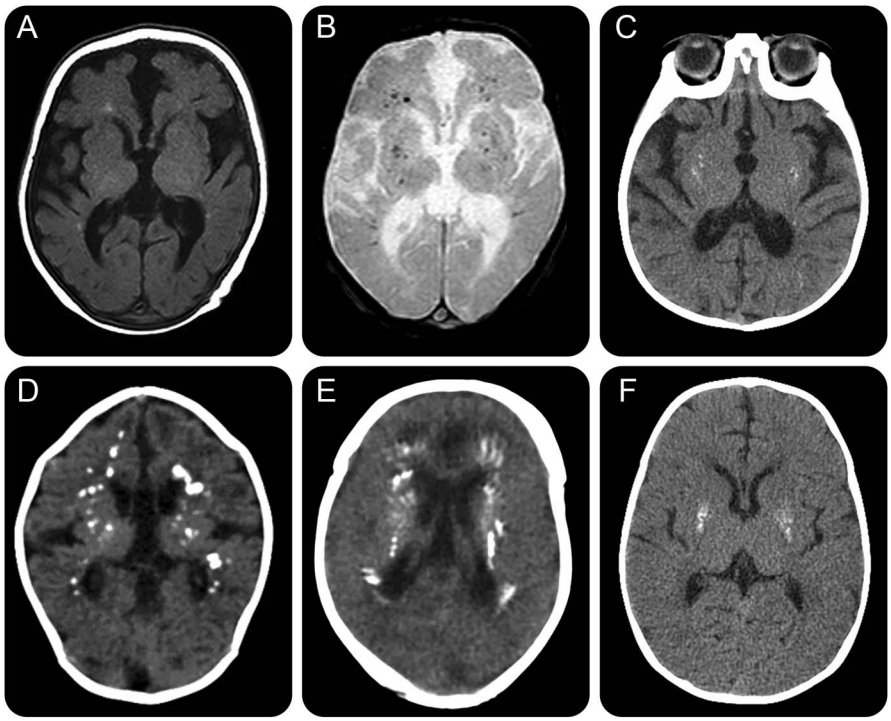
MRI and CT data were available for 86 patients, MRI only in 23, and CT images only in 12. Follow-up examinations were available for 56 subjects (46.3%, mean duration 14.5 months, range 0.5–144).

The clinical severity scores ranged from 3 to 15. Eighty-four patients (69.4%) had a total score $\geq$12.

Classic neuroradiologic criteria. Brain calcifications were present in 110 subjects (90.9%) (figure 1). We could not confirm the presence or absence of calcifications in 9 patients (7.4%) for whom neither CT images nor CT reports were available, and for whom MRI did not show the presence of calcifications. Calcification was apparent on MRI in 64 subjects (58.2%; 64/110) (figure 1, A and B). In 3 of the 23 cases for whom CT scan images were not available, a previous CT radiologic report described the presence (2 cases) or the absence (one case) of calcification.

Table 1 reports the localization and relative frequency of the intracranial calcifications. Calcifications were usually spot-like and limited to the most classical localizations (lentiform nuclei, deep white matter) in 83 of the 110 subjects (75.5%) (figure 1C). Severe calcifications were observed in 27 patients (24.5%) (figure 1D). Seven of 8 patients with *ADAR1* mutations had striatal calcification (figure 1F). Calcification was observed along the walls of the cystic lesions in 2 patients with lobar white matter cysts. In 3 patients, calcification was not present on

Figure 1 Calcifications in our sample of patients with Aicardi-Goutières syndrome



Calcium deposits could be visualized on axial T1-weighted (A) and T2-weighted gradient-echo images (B). (C) Spot-like calcifications located in the lentiform nuclei and left posterior white matter. (D) Severe confluent calcifications. (E) Linear pattern. (F) Calcifications limited to the putamina in a patient with *ADAR1* mutations.

the first examination, but appeared on follow-up less than 1 year after clinical presentation. In 5 subjects, severe and progressive calcification developed during follow-up.

Various degrees of cerebral atrophy were documented in 111 subjects (91.8%). As noted before,[16] the cortex was relatively spared and atrophy was attributed to white matter loss. Basal ganglia atrophy was documented in cases with bilateral striatal necrosis. Cerebral atrophy became worse in 20 of the 56 (35.7%) subjects observed longitudinally. In 4 patients, the degree of atrophy decreased during follow-up; in 2 of these patients, the improvement of atrophy was associated with progressed myelination (figure 2, H and I). In 2 patients, the initial scan did not show atrophy, but this developed on follow-up at 3 and 19 months, respectively.

Table 1 Localization and frequency of intracranial calcifications in our sample of patients with Aicardi-Goutières syndrome

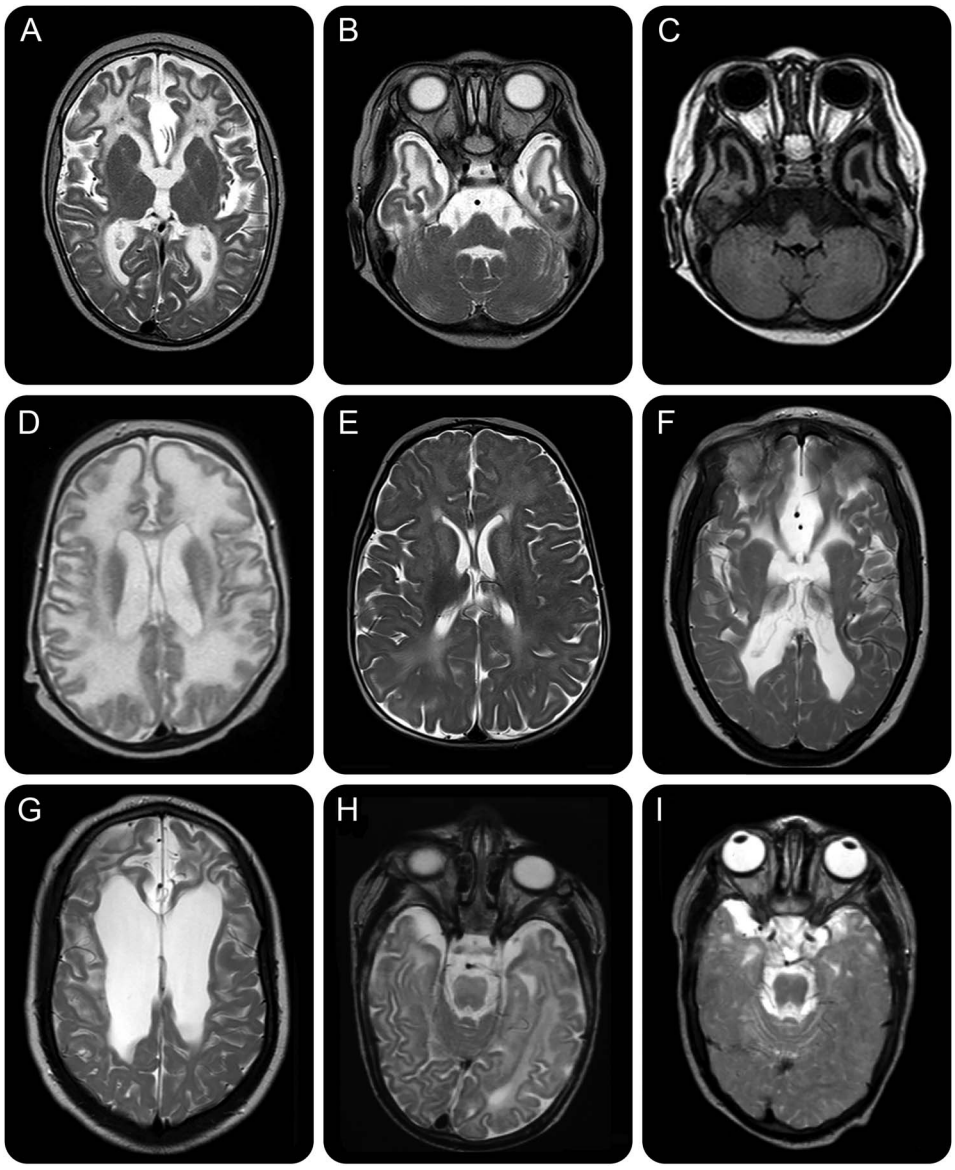
	No. (%) (total n = 110)
Basal ganglia	85 (77.3)
Striatum	7 (6.4)
White matter	81 (73.6)
Thalamus	24 (21.8)
Cerebellum	28 (25.5)
Dentate	16 (14.5)
Cerebellar white matter	12 (10.9)
Brainstem	11 (10.0)
Internal capsule	2 (1.8)
Cortex	1 (0.9)
Corpus callosum	1 (0.9)
Eye	1 (0.9)

Multiple localizations are possible.

White matter involvement was present in 120 children (99.2%). The one exception was a patient with bilateral striatal necrosis secondary to *ADAR1* mutations and AGS clinical phenotype. The leukoencephalopathy worsened during follow-up in 13 cases (13/56; 23.2%), with the development of frontotemporal white matter rarefaction in 4. Ten of these 13 patients underwent the first MRI before age 6 months and shortly after disease onset.

MRI patterns of leukoencephalopathy. A detailed analysis of the white matter involvement was performed on the 108 patients with leukoencephalopathy and available MRI data. We confirmed the presence of 2 main patterns of involvement: a frontotemporal predominance in 55 (50.9%) (figure 2, A–C) and a diffuse involvement in 45 subjects (41.7%) (figure 2D). We documented a new leukoencephalopathy

Figure 2 MRI patterns of white matter involvement



(A, B) Axial T2-weighted image shows frontotemporal predominance in a 21-month-old patient. (C) Axial T2-weighted fluid-attenuated inversion recovery image shows bilateral white matter rarefaction at the level of the temporal poles in the same patient reported in A and B. (D) Axial T2-weighted image shows diffuse pattern and swollen frontal poles in a 4-month-old patient. (E) Axial T2-weighted image shows periventricular predominance in a 12-month-old patient. (F, G) Axial T2-weighted images show periventricular white matter involvement and loss of substance in a 3-year-old patient. (H, I) Axial T2-weighted images show improved atrophy and myelination in a patient at 3 months (H) and 5 years of age (I).

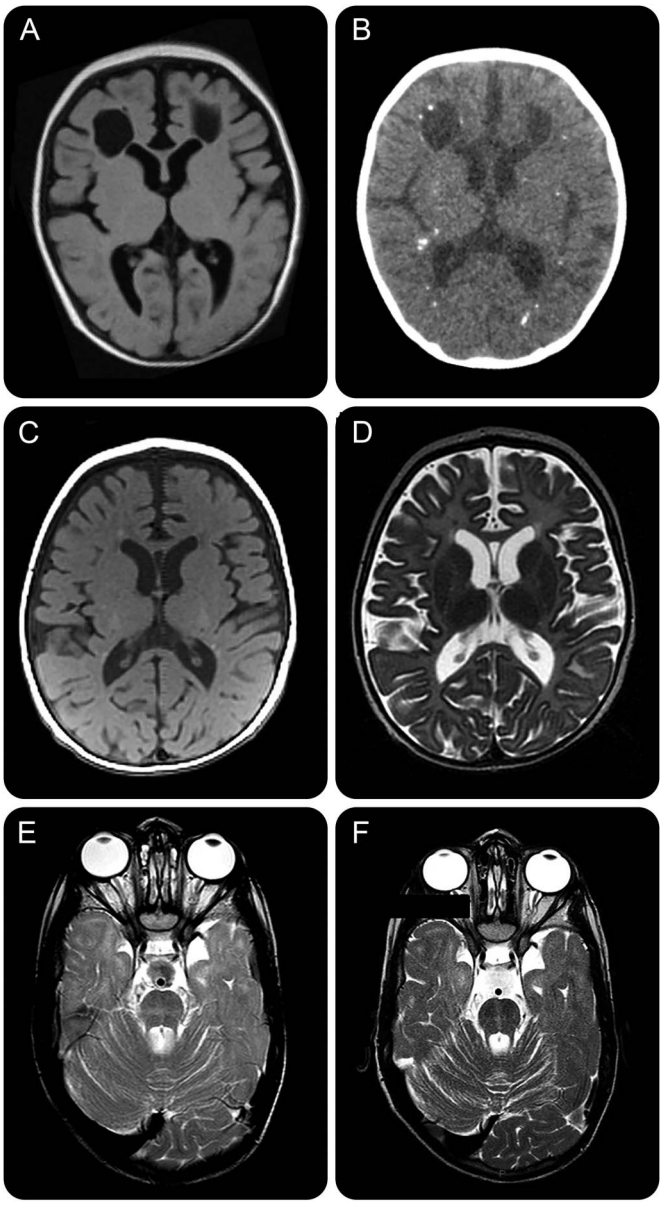
pattern characterized by periventricular predominance in 8 patients (7.4%) (figure 2, E and F).

In 5 patients (3.7%) with diffuse or periventricular involvement and with onset of disease prior to 3 months of age, we documented significant loss of white matter volume at the level of the occipital and frontal horns of the lateral ventricles (figure 2, F and G).

White matter rarefaction, a well-known feature of AGS, was documented in the frontal or temporal poles of 54 subjects (50.0%) (figure 2C). A novel radiologic feature was the presence of deep white matter cysts observed in 7 subjects (6.5%) (figure 3, A and B), 4 of which (57.1%) carried mutations in the *TREX1* gene. These white matter cysts are located in the deep white matter and they are well-defined, as opposed to white matter rarefaction that commonly involves ill-defined areas of U-fibers of the temporal and frontal poles. Calcification along the borders of the cysts was present (figure 3B). In one *TREX1*-mutated patient, intraventricular blood was an additional finding.

The leukoencephalopathy was commonly diffuse and homogeneous. However, we observed patchy

Figure 3 Novel neuroradiologic findings in Aicardi-Goutières syndrome



(A) Axial T2-weighted fluid-attenuated inversion recovery shows deep frontal white matter cystic lesions in a 4-month-old patient. (B) CT scan shows calcifications along the walls of the cysts. (C) Axial T1-weighted and (D) T2-weighted images show inadequate myelination in an 8-month-old patient with mild white matter involvement. (E, F) Axial T2-weighted images performed in a patient at age 4 and 7 years show involvement of the transverse pontine fibers.

white matter involvement in one case with *RNASEH2A* mutations.

Myelination inadequate for age was present in 30 patients (27.7%), whose mean age at the time of MRI was 6.9 months (range 1–47 months) (figure 3, C and D). We observed a progression of myelination over time in all 22 patients with available follow-up MRI data (22/30; 73.3%).

Other findings. As recently reported,[23,24] bilateral striatal necrosis was documented in 5 patients (62.5%) of the 8 with mutations in *ADAR1*. The calcifications were specifically localized in the striatal nuclei, though not exclusively. Seven (87.5%) of the 8 *ADAR1* patients also had leukoencephalopathy. A single patient did not have any white matter abnormalities at the time of the MRI, when she was 9 months old.

Vascular lesions, such as intracranial aneurysms or dysplastic vessels, were documented in 6 of the 12 patients (50.0%) with *SAMHD1* mutations. In addition, a vascular lesion was found in one patient with *TREX1* mutations and antiphospholipid syndrome.[22]

Pontocerebellar hypoplasia was documented in 6 patients (5.0%). Brainstem signal abnormalities were noticed in 3 patients (1.7%): one of them presented with an acute, probably ischemic lesion in the pons; in another patient, the transverse pontine fibers were involved (figure 3, E and F); and in the third patient, the abnormal signal raised the possibility of a low-grade glioma, which was not proven (no follow-up data).

Association among neuroradiologic findings, clinical data, and genotype. Statistically significant results are reported in table 2 and summarized below; the results without statistically significant association are reported in table e-2.

Frontotemporal white matter rarefaction was strongly associated with mutations in *TREX1* and an age at onset less than 3 months. However, when correcting for the mutated gene, the association was not statistically significant. Severe calcification was also associated with *TREX1* mutations and age at onset less than 3 months. In this case, when correcting for the mutated gene, the association persisted. Conversely, AGS due to *RNASEH2B* mutations was inversely associated with severe calcification.

The presence of delayed myelination was associated with mutated *RNASEH2B* and age at onset less than 3 months. When correcting for the mutated gene, the association between delayed myelination and early age at onset persisted.

The severity of the clinical picture was associated only with a pattern of frontotemporal predominance. This association was documented when analyzing the variable as dichotomous ($<$ vs $\geq$12) and as continuous. When corrected for the mutated gene, the association was consistent.

DISCUSSION This is the largest study of neuroradiologic findings in AGS yet reported, and takes into account the full spectrum of genotypes as currently described. Our study is the result of a long-term international collaboration that has enabled the identification of a large number of patients with genetically confirmed AGS and description of the associated MRI and CT features.

Table 2 Statistically significant results of the logistic regression analysis performed between selected neuroradiologic findings and genetic/clinical data

	Neuroradiologic feature	OR	95% CI Lower	95% CI Upper
Mutated gene				
TREX1	Frontotemporal rarefaction	7.197	2.246	23.059
TREX1	Cysts outside the frontotemporal regions	8.526	1.453	50.026
TREX1	Severe calcifications	6.964	2.401	20.198
RNASEH2B	Severe calcifications	0.248	0.089	0.688
RNASEH2B	Delayed myelination	3.022	1.214	7.526
RNASEH2A	Periventricular pattern	6.333	1.010	39.706
SAMHD1	Periventricular pattern	8.719	1.654	45.948
Clinical feature				
Age at onset <3 mo	Frontotemporal rarefaction	3.3	1.359	8.015
Age at onset <3 mo	Severe calcifications	17.683	2.266	137.989
Age at onset <3 mo[a]	Severe calcifications	10.548	1.276	87.221
Age at onset <3 mo	Delayed myelination	4.909	1.348	17.875
Age at onset <3 mo[a]	Delayed myelination	8.696	2.117	35.714
Age at onset <3 mo	AP pattern	3.071	1.292	7.304
Age at onset <3 mo[a]	AP pattern	3.539	1.298	9.651
Total score >12	AP pattern	6.143	1.262	29.895
Total score >12[a]	AP pattern	9.925	1.926	51.146
Total score (continuous)	AP pattern	1.286	1.019	1.622
Total score (continuous)[a]	AP pattern	1.402	1.085	1.812

Abbreviations: AP = anteroposterior; CI = confidence interval; OR = odds ratio.
[a] Analysis corrected for the mutated gene.

AGS neuroradiologic phenotype is expanding. In light of the new phenotypes recently observed in patients with mutations in certain AGS-associated genes,[10,15] the conclusions of this study apply specifically to patients with a classical diagnosis of AGS[11,17] or with mutations in one of the AGS genes and clinical phenotype reminiscent of AGS as previously defined.

As the neuroradiologic features that were the object of our study are also recognized diagnostic criteria for AGS, a limitation of our work is the presence of a potential ascertainment bias. This is why we performed a descriptive analysis without any predictive value.

Leukoencephalopathy, calcification, and cerebral atrophy are still valid diagnostic criteria for AGS, as they are present in almost all subjects. The detection of calcification remains an important clue.[10,15] Our study demonstrates that MRI could detect calcification—especially when gross and numerous—in more than half of cases. Thus, we suggest that GRE or SWI sequences be added to the diagnostic protocol of patients with a disorder for which AGS is in the differential diagnosis. Nonetheless, even a single calcification can suggest AGS; therefore, CT scan should be performed when the clinical and MRI data are consistent with a diagnosis of AGS and the MRI does not reveal calcium deposits. CT and MRI provide complementary information and, ideally, should be performed at the same time.[17]

Our study confirms that leukoencephalopathy presents with either a frontotemporal predominance or a diffuse pattern.[16] In addition, we identified a third pattern of white matter involvement characterized by periventricular predominance associated in a few cases with an enlargement of the occipital and frontal horns of the lateral ventricles, due to white matter loss. The enlarged lateral ventricles with scalloped margins are reminiscent of periventricular leukomalacia; therefore, AGS should be considered in the differential diagnosis of subjects with MRI findings interpreted as periventricular leukomalacia and an unremarkable prenatal or perinatal history. The fact that, in our patients with AGS, the entire white matter was abnormal including the subcortical regions argues against the diagnosis of periventricular leukomalacia.

White matter rarefaction localized in the frontal and temporal poles, often associated with swelling, is confirmed as common in AGS.[16,28] Moreover, we described the new finding of lobar white matter cysts, deeply located and well-defined. The presence of calcifications around the borders of these lesions suggests a distinct pathogenic process.

Previously, multifocal white matter involvement has never been associated with AGS. However, the identification of patchy white matter involvement in one child with *RNASEH2A* mutations suggests that this appearance should not exclude a diagnosis of AGS. Similar atypical cases are reported in the literature.[13,14] In this context, the detection of calcification might serve as a useful diagnostic pointer.

A further novel radiologic feature was the evidence of inadequate myelination observed in almost one third of patients, the majority of whom underwent MRI examination in the first year of life. In all patients with follow-up MRI, myelination progressed. These observations suggest that in AGS the white matter involvement is not due to a primary disorder of myelination. Nonetheless, myelination is affected by the AGS pathogenetic process, particularly when the disease starts early in life. This finding is not unexpected, as inadequate myelination is often observed in early-onset neuronal degenerative disorders.[29–31] The recognition of key neuroradiologic features enables an early diagnosis of AGS and consequently prompt genetic counseling. In addition, the

progressive nature of AGS is specific of the initial period of disease course; therefore, an early diagnosis can be crucial in case potential therapies will become available to stop or prevent the further progression of the disease in its initial stages.

The various radiologic phenotypes documented in this study expand the traditional differential diagnosis of AGS, which includes congenital infections (especially cytomegalovirus) and genetic leukoencephalopathies with white matter rarefaction or cysts and calcification (e.g., *RNASET2*-deficient leukoencephalopathy[32]).

Interestingly, we observed the improvement of cerebral atrophy in some subjects. These findings suggest that in AGS the disease is active in a time-limited way at the end of which the disease burns out, even if patients continue to demonstrate an interferon signature.[26]

The heterogeneity of neuroradiologic patterns reflects the timing of the disease onset and the complex pathogenesis, which includes inflammatory and autoimmune mechanisms. However, much has yet to be explored. Specifically, each AGS gene has different functions; therefore, we can expect differences in the pathogenesis and ultimately in the neuroradiologic picture in relation to the mutated gene.[9,19,21,23,24] We observed a significantly higher prevalence of frontotemporal white matter rarefaction and severe calcification in patients with *TREX1* mutations and early age at onset. Mutated *TREX1* was also associated with cysts outside the frontotemporal region. It is unclear whether these findings are more common in patients with *TREX1* mutations because of a distinct pathogenesis, or because of early disease onset, which is more frequent in *TREX1*-mutated patients. The fact that these patients are typically symptomatic at the time of birth indicates a prenatal onset of disease and perhaps a particular susceptibility of the brain to interferon exposure in utero.[10] Indeed, the association between severe calcification and early onset of the disease was confirmed after correcting for the mutated gene, thus suggesting that the more immature the brain, the more vulnerable it is to AGS pathogenic processes. Except for the presence of frontotemporal pattern of leukoencephalopathy, no other statistically significant associations were found between all the neuroradiologic features and the clinical severity. This analysis was limited by the fact that the large majority of our patients were severely affected.

We presented an update of the neuroradiologic features of AGS performed on the largest cohort of genetically confirmed patients reported to date. Besides the classic neuroradiologic picture, we have described new patterns and findings that illustrate the widening phenotype of AGS. In spite of recent advances,[33] there is still much not understood about the AGS pathogenesis and this is reflected in the spectrum of radiologic features described here.

AUTHOR CONTRIBUTIONS

Roberta La Piana: writing the manuscript, study concept and design, analysis and interpretation of data. Carla Uggetti: study concept and design, analysis and interpretation of data, revising the manuscript for content. Federico Roncarolo: statistical analysis and interpretation of data, revising the manuscript for content. Adeline Vanderver: analysis and interpretation of data, acquisition of data, revising the manuscript for content. Ivana Olivieri: analysis and interpretation of data, acquisition of data. Davide Tonduti: analysis and interpretation of data, revising the manuscript for content. Guy Helman: analysis and interpretation of data, acquisition of data. Umberto Balottin: revising the manuscript for content. Elisa Fazzi: revising the manuscript for content, acquisition of data. Yanick J. Crow: revising the manuscript for content, acquisition of data. John Livingston: study concept and design, analysis and interpretation of data, revising the manuscript for content, acquisition of data. Simona Orcesi: study concept and design, analysis and interpretation of data, revising the manuscript for content, acquisition of data.

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