Original article

Abnormal myelination in Angelman syndrome

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ARTICLE INFO

ABSTRACT

Patients with Angelman syndrome (OMIM # 105830) are generally thought to have normal brain imaging studies except for occasional minor cerebral atrophy. We report 9 patients with genetically proven Angelman syndrome, who were examined by magnetic resonance imaging (MRI) between the ages of 7.5 months and 5 years. MRI in the 5 patients examined during infancy revealed myelination delay and a deficit of white matter. Retarded and/or abnormal myelination in Angelman syndrome seems to be a common finding that may be diagnostically misleading. This is particularly important in the evaluation of infants with possible Angelman syndrome, who present with nonspecific clinical features and have not yet developed the characteristic behavioural, language, and movement abnormalities.

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1. Introduction

Angelman syndrome (AS; OMIM # 105830)[1] is clinically characterized by mental retardation, speech impairment, paroxysms of laughter and other unique, bizarre behaviour, as well as different degrees of ataxia, jerky movements, and pyramidal signs. Affected children have a normal prenatal history and are normal at birth, developmental delay becoming evident in severe cases during the very first months of life, in moderate cases by 6–12 months. Decelerating head growth generally results in microcephaly by the age of 2 years. Seizure onset commonly occurs after the age of one, while severe speech deficit, characteristic behavioural traits, and ataxia become evident later. Infants with AS therefore present a rather unspecific phenotype with the major clinical finding of developmental delay.

AS is caused either by de novo deletions of maternal 15q11.2-q13 (70% of cases), paternal uniparental disomy (2–3%), imprinting defects (3–5%) of this region, or by mutations involving the gene coding for ubiquitin protein ligase E3A (UBE3A) at the same chromosomal location (5–10%).[2]

In an infant or a young child presenting with retarded psychomotor development, brain imaging is often performed in order to search for underlying brain abnormalities or associated signal changes. In general, brain imaging findings in AS are thought to be normal except for occasional minor cerebral atrophy.[3] Abnormal myelination is not a finding usually associated with AS and may consequently be diagnostically misleading.

The initally unexpected and diagnostically misleading finding of abnormal myelination in 2 patients alerted us to the possible occurence of white matter changes in AS.

We have therefore reviewed brain imaging findings in the 20 patients with genetically confirmed AS seen at the department of neuropaediatrics between 1995 and 2007. In 9 of these, MRI had been performed and was available for evaluation. 5 patients had not undergone any brain imaging procedure. Externally performed CT and MRI examinations in 2 and 4 patients, respectively, were not available for review.

2.   Patients and methods

All 9 patients presented towards the end of the first year of life with delayed psychomotor development. They are being clinically followed at our institution and have since developed the typical clinical picture of Angelman syndrome.

AS was confirmed by molecular genetics in all 9 patients, demonstrating a typical methylation pattern with lack of maternal imprint of 15q11.2-13 in 8 of 9 children (patients 1–7, 9). The genetic mechanism of AS was further investigated in 4 patients, revealing a deletion of maternal chromosome 15q11.2-13 in 3 patients (patients 2,3,5). One child carried an UBE3A point mutation (patient 8). Postinfectious and metabolic diseases were ruled out in all patients.

Age at MRI and MRI findings are summarized in Table 1. In the following part the clinical picture of those 5 infants with abnormal myelination is described at the time of MRI.

In patient 1 an MRI scan was obtained at the age of 7.5 months. At that age, head circumference was just below the 3rd percentile (P3), length at P3–10, weight at P3. She was known for a persistent ductus arteriosus and vesicoureteral reflux with ureter stenosis and repeated urinary tract infections. Development was clearly delayed: The child did not reach for objects and fixation was inconstant. Muscle tone was clearly reduced, sitting or turning over was not possible. Diagnosis of Angelman syndrome was made at the age of 9 months. EEG at that time showed abnormal theta rhythms. Epilepsy with tonic seizures started at age of 17 months and was difficult to treat.

Patient 2 underwent MR imaging aged 8 months and AS was diagnosed at that time. His psychomotor development was severely delayed: He did not transfer objects from hand to hand, he could neither roll over nor sustain a sitting position. He was continually in motion with jerky movements. His muscle tone was normo- to hypotonic; tendon reflexes were normal and pyramidal tract signs absent. Head circumference was at P10, body length at P50. EEG demonstrated dominant theta acitivity and – during sleep – very irregular spike-wave complexes resembling hypsarrhythmia.

MRI was performed in patient 3 at the age of 12 months. Clinically, he was a self-absorbed child with severe developmental delay. At that stage, age corrected head circumference had dropped from P25 at birth to below P3. There was slight truncal hypotonia, movements of the arms were jerky. Tendon reflexes were normal, pyramidal tract signs absent. EEG revealed high amplitude mixed theta–delta activity with intermittent posterior theta activity. Diagnosis of AS was made several months later.

In patient 4 an MRI scan was performed at the age of 17 months when diagnosis of AS was made as well. Aged 16 months, she had been able to sustain a sitting position and had just begun to crawl. Aged 18 months, her movements were jerky, muscle tone and tendon reflexes were normal. Head circumference had decreased from just below P50 at birth to P25 at 17 months. EEG was characterized by dominant theta activity with intermittent posterior large amplitude slow spike waves. The mother described short spells with loss of reaction and myoclonic jerks responding well to valproic acid.

MRI in patient 5 was performed at the age of 18 and 25 months. AS was diagnosed several months later. At the age of 18 months, microcephaly was already present (head circumference 2.5 cm < P3; length P50, weight 1.5 kg < P3). Muscle hypotonia was present and tendon reflexes were brisk. She learned to walk without support at the age of 3 years, active speech was still absent. Epilepsy with short tonic seizures started at age of 3.5 years; seizures responded promptly to valproic acid and clobazam.

MR examinations consisted of axial spin echo (SE) double-echo and T1- or T1IR-weighted (w) sequences as well as a sagittal T1w gradient echo sequence (Philips Gyroscan 0.5 Tesla) in all patients but patient 6, of whom only T2w turbo spin echo (TSE) but no spin echo images were available.

All 10 MR examinations of the 9 patients were retrospectively reviewed with consensus reading by 2 experienced paediatric neuroradiologists (IH, AS) and brain myelination stage was assessed according to myelination time tables.[4,5]

Table 1 – Summarized findings of the 10 cranial MRs of the 9 patients with Angelman syndrome (age = patients' age [months] at time of MRI; wm = white matter)

Patient	Age	Myelination	Myelination stage	wm Signal alterations	Corpus callosum	Ventricles
1	7.5	Delayed	5–6 mo	–	Uniformly thin	++
2	8	Delayed	5–6 mo	–	Uniformly thin	++
3	12	Delayed	8 mo	Slightly patchy	Dorsally thinned	++
4	17	Delayed	10 mo	Par.occ. white matter	Mildly thinned	++
5	18	Delayed	10 mo	Par.occ. white matter	Irregularly thinned	Normal
6	23	Normal	Complete	Par.occ. white matter	Mildly thinned	+
5	25	Delayed	12 mo	Par.occ. white matter	Irregularly thinned	Normal
7	29	Normal	Complete	Par.occ. white matter	Mildly thinned (ventral)	+
8	34	Normal	Complete	Par.occ. white matter	Normal	Normal
9	61	Normal	Complete	Par.occ. white matter	Mildly thinned (ventral)	+

3.   Results

Myelination in patients 1 and 2, aged 7.5 and 8 months, respectively, was retarded and corresponded to a stage normally observed by 5–6 months.[4,5] The corpus callosum was still of a uniform size and appeared too thin for the patients' age but normal for a 5–6-month old child (Fig. 1).

The prominent, initially misleading MR finding in patient 3 was abnormal and retarded myelination which at the age of 12 months corresponded to that normally observed at 8 months (Fig. 2). Additional signs of a white matter disorder consisted of patchy T2 hyperintensity of the periventricular and deep white matter and a dorsally thinned corpus callosum.

In patients 4 and 5, myelination at ages 17 and 18 months, respectively, was more severely retarded and corresponded to a myelination status of approximately 10 months (Fig. 3). The corpus callosum was slightly thin in patient 4; in patient 5 it appeared slightly irregular with a relatively thin genu and an anterior zone of thinning. Circumscribed T2 hyperintensity of the parieto-occipital white matter in patients 4 and 5 may correspond to the normal finding of the so-called terminal zones of myelination, although it reaches the ventricular border. Follow-up MRI in patient 5 at 25 months revealed only minor progression of myelination, otherwise the patient's brain appeared unchanged.

In all 5 patients with myelination delay, thinning of the corpus callosum and in 4 patients widening of the ventricles indicated supratentorial atrophy with a deficit of myelinated white matter. In patient 4 the normal variant of a cavum Vergae was present.

Table 1 summarizes MR findings of all 9 patients organized by age at MRI. Patient 6 was the only patient examined with a T2 turbo spin echo (TSE) sequence, which is less sensitive for white matter signal changes compared to a spin echo (SE) sequence. Although myelination on his T2w TSE images appeared to be complete, some deficit might be missed due to the sequence used. Myelination in the 3 older patients examined with T2w SE sequences was complete (patients 7–9). Again, a mildly thinned corpus callosum in conjunction with slight widening of ventricles indicated a discrete deficit of supratentorial white matter and white matter tracts crossing in the corpus callosum. All patients examined after infancy had in common symmetrical T2 hyperintensity of the parieto-occipital periventricular white matter without corresponding signal alteration on T1w images compatible with the so-called terminal zones.

4.   Discussion

Clinical and EEG findings in our patients suggested the diagnosis of Angelman syndrome, which was consecutively confirmed by genetic testing. MRI did rule out brain malformations, but revealed the potentially misleading finding of myelination delay and a deficit of white matter in those patients examined as infants.

Reviewing the literature on Angelman syndrome with regard to brain imaging, the majority of patients are reported to have either normal findings or a minor degree of brain atrophy[3,6–15] (Table 2). This may be partly due to the fact that in most reported patients computed tomography (CT) scans were performed that have a much lower sensitivity for white matter changes compared to MRI. One of the patients in whom a CT scan was performed was reported to have white matter changes, described as focal periventricular hypodensity.[3] Among the reported patients examined by MRI, white matter abnormalities were described in only one case,[9] an 11-month old patient with T2 hyperintensity of the frontal and occipital periventricular white matter. Molfetta et al.[14] showed one T2w image of a 5 year old patient who, in addition to minor atrophy, shows evidence of deficient and/or abnormal myelination. While the corpus callosum and internal
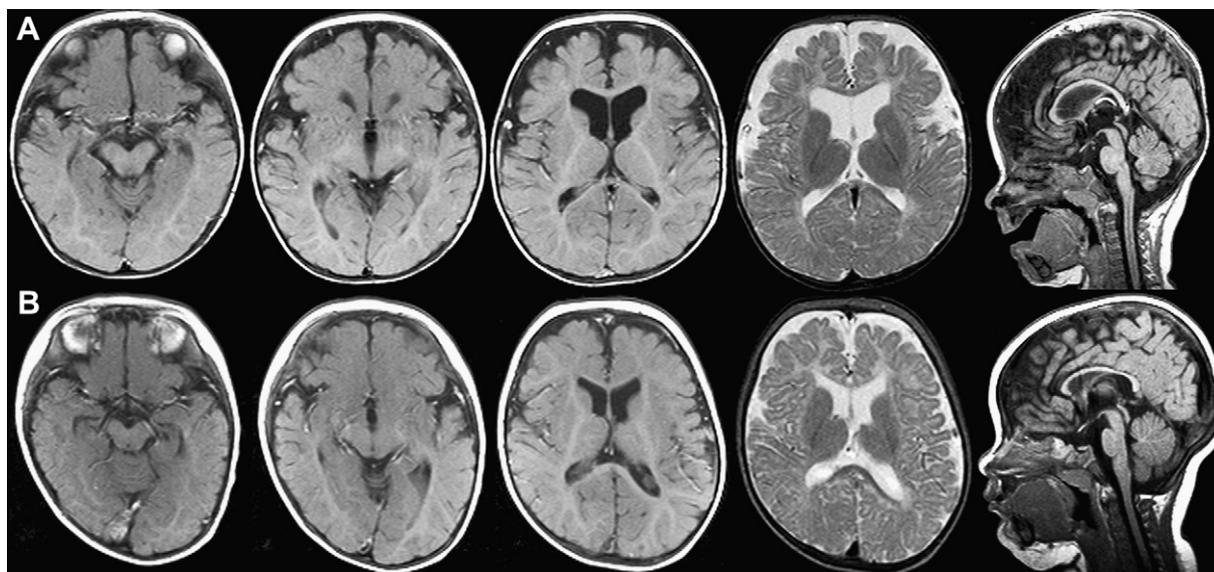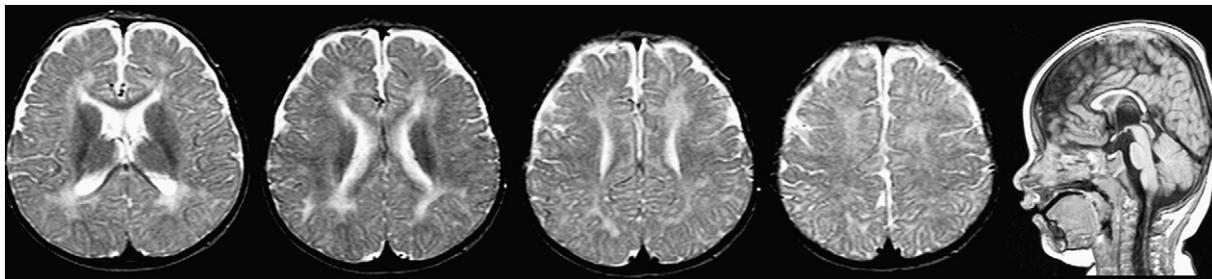

Fig. 1 – MRI of patients 1 (A) and 2 (B) at age of 7.5 and 8 months. Myelination on T1w is still deficient in the frontal and temporal white matter and the corpus callosum is still uniformly thin, corresponding to a maturation stage of 5–6 months.

Fig. 2 – MRI of patient 3 aged 12 months revealing myelination delay (stage ∼ 8 months), a dorsally thin corpus callosum and a slightly patchy T2 signal of the white matter. Myelination appeared complete on T1w images (not shown). On T2w images the hypointense signal of myelinated white matter is present in the genu and the splenium of the corpus callosum, and the anterior limb of the internal capsule. These findings are consistent with a myelination status of 8 months or more. The signal cross over between gray and white matter, however, has not yet progressed beyond the stage usually observed by 8 months. Cortex and adjacent white matter are still isointense throughout most of the brain, excepting the perirolandic area and the optic radiation.

capsule demonstrate the normal signal of myelinated white matter, myelination of at least the frontal white matter is still deficient or abnormal. These changes were not commented upon in their report.

While the literature is so scarce it is interesting that the "Angelman Syndrome Consensus Diagnostic Criteria"[16] not only require "a structurally normal brain using MRI or CT", but also mention possible dysmyelination – this however,
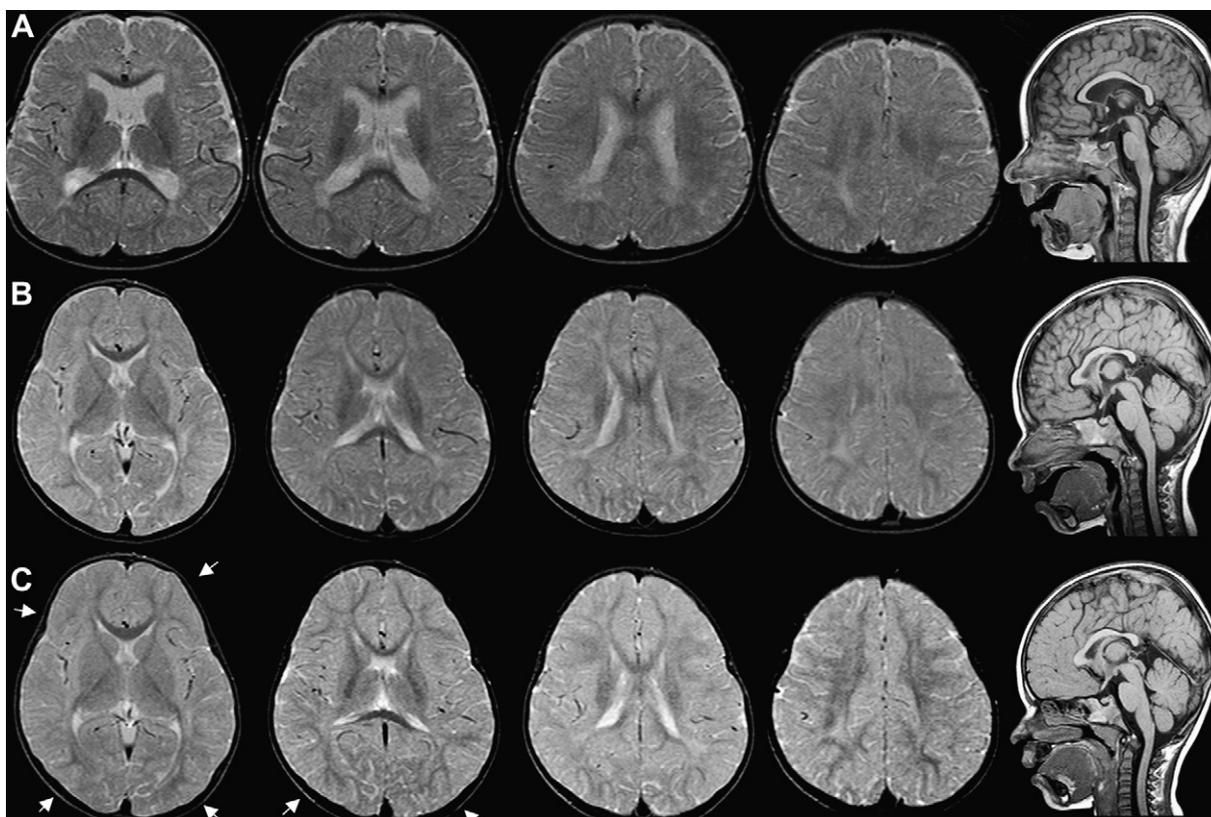
Fig. 3 – MRI of patients 4 (A) and 5 (B; C) aged 17 (A), 18 (B), and 25 (C) months, respectively. The internal capsule and the corpus callosum show the normal T2 hypointense signal of myelinated white matter present from 8 months onwards, but the contrast inversion between cortex and white matter has not progressed beyond a myelination stage of 10 months (A, B). Mild thinning of the corpus callosum and widened ventricles are seen in patient 4 (A), a slightly irregular outline of the lateral ventricles and irregular thinning of the splenium and anterior corpus callosum in patient 5 (B, C). On follow-up, patient 5 reveals a discrete progression of myelination (arrowheads) in the peripheral white matter of parietal, occipital, and frontal lobes (C).

Table 2 – Brain imaging findings in AS reported in the literature

Author	Patients	CT	MRI	Normal	Atrophy	Others
Clayton-Smith, 1993[3]	57	57		35	19	1× suggestive of migrational abnormality 1× periventricular hypodensity 1× left temporal arachnoid cyst
Williams, 1982[6]	4	4		1	2	1× "unilateral cerebellar atrophy"
Dörries, 1988[7]	7	7		2	5	–
Williams, 1989[8]	2	2	2	1	1	2/2 Brachycephalus + ↑ foramen magnum (transv. diameter)
Yamada, 1990[9]	1		1		1	Focal ↑T2 areas: front. + occ. white matter, left int. capsule
van Lierde, 1990[10]	1	1	1		1	Left temporal arachnoid cyst
Incorpora, 1994[11]	1	1	2		1	Cystic dilatation of post. vermian cistern
Young, 1994[12]	1		1			Pituitary cyst
Mastroyianni, 2002[13]	1		1	1		Associated split cord malformation
Molfetta, 2004[14]	1		1		1	*Abnormal white matter (not commented on)*
Meyer Witte, 2005[15]	1		1			Intracranial aneurysm

without citing any references. The frequency and natural course of white matter changes in AS are not commented on or reported elsewhere.

Although the largest group of patients with AS and MRI reported so far, the number of our patients is insufficient to estimate the incidence of myelination changes and we can only speculate on the natural course of the changes observed. Nevertheless it is noteworthy that delay of myelination was present in all infants and that myelination tended to be complete in the older children. This suggests that in infants with AS there is retarded brain maturation as reflected by myelination delay, whereas a deficit of white matter, evidenced by a thinning of the corpus callosum and mildly widened ventricles, is observable in infants and in children. Whether the very frequent occurence of parieto-occipital white matter changes in our patients with AS is incidental and attributable to so-called terminal zones of myelination or whether it rather indicates additional dysmyelination is open to speculation. So-called terminal zones are frequent findings in neurologically normal and impaired children. A although they classically should not reach the ventricular border, this differentiating criterion is not highly reliable.

It may be possible that the different genetic mechanisms of AS influence myelination differently as there is a genotype–phenotype correlation regarding the severity of neurological symptoms in AS with deletions leading to the severe forms of AS.[17] Our series is too small to distinguish between these subtypes of AS; larger studies are needed to clarify that point. There are no genes with an obvious impact on myelination in the region deleted in AS. The possible mechanism of the phenomenon we observed in our patients remains therefore to be elucidated.

The MRI changes observable in our patients with AS – myelination delay, a deficit of white matter, and focal white matter signal abnormalities – are not specific and may be observed in other chromosomal or neurometabolic disorders.[18–20] The diagnosis of AS is based on the clinical picture and EEG findings and supported by genetic testing. It does neither require nor rely on brain imaging. Nevertheless, infants with AS presenting with as yet "unspecific developmental delay" will often undergo MRI to search for underlying brain abnormalities or signal changes.

Our observations indicate that delayed myelination, white matter volume reduction, and focal white matter signal abnormalities are a much more common finding in Angelman syndrome than expected. They substantiate the consensus criteria's suggestion of possible white matter changes and emphasize that signs of a white matter disorder should not be regarded as evidence against the diagnosis of Angelman syndrome.

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