What would the brain look like in Angelman syndrome?

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Scientific knowledge relies on sound evidence. In many domains the latter is still erratic, so that the former is provisionally replaced by inference based on scant data provided unsatisfactorily answered questions remain critically open for scrutiny. Neuroimaging and pathology of Angelman syndrome1 provide an illustration of this process.

Although this condition is primarily characterised by various aspects of brain dysfunction and despite the relatively good availability of neuroimaging techniques in centres where the syndrome has been extensively studied for several dozens of years, there have been surprisingly few neuroimaging studies. Harry Angelman described the skull X-ray and pneumoencephalogram of his three patients when he first characterised the syndrome in 1965.2 Skull X-rays were normal, excluding craniosynostosis as a cause for the patients' microcephaly; air encephalograms showed slight ventricular dilatation in all children and increased presence of air around the cortex, suggesting mild cortical-subcortical atrophy. These techniques have become obsolete with the advent of computed tomography and of course magnetic resonance imaging (MRI). In their aetiological work-up for developmental delay or epilepsy, many patients undergo MRI before the diagnosis of Angelman syndrome is established, allowing for at least retrospective studies but even those have been extremely limited. The general, largely uncontrolled experience with structural imaging techniques has been a lack of abnormalities except for eventual, mild to moderate non-specific cerebral atrophy and more rarely cerebellar atrophy. In this issue of the European Journal of Paediatric Neurology, Harting and her colleagues present a retrospective MRI study involving nine children with Angelman syndrome,3 i.e. the largest group studied to date in this way although several hundreds of patients have been reported and many more diagnosed over more than 40 years. Interestingly, they report white matter changes in most of these patients and additional findings suggestive of a delay in the myelination process, white matter volume reduction or focal abnormalities in myelinated areas. In their review of the literature, they mention two previous cases of abnormal signal in the white matter. Dysmyelination was also noted in a few other patients.4,5 Anticipating while somewhat overshooting Harting et al.'s view of a more common finding than expected, it was even suggested to be typical of Angelman syndrome some 15 years ago.6 In order to test this hypothesis, more systematic studies are urgently needed.

Perhaps even more surprising than the paucity of neuroimaging studies, there have been neuropathological reports on only two patients to date, both published more than 15 years ago. They were obtained in a general context of disinclination for in autopsy in medical practice which has further declined since then. One concerns a 21 year-old woman with a history of severe epilepsy who died in a context of pneumonia.7 It does not describe any supratentorial dys- or demyelination but a loss of both myelin and axons in the cerebellar white matter thought to be secondary to seizures or antiepileptic treatment. The other neuropathological study concerns a 3 year-old boy who died of asphyxia presumably secondary to a seizure and shows no evidence of white matter abnormality.8

In conclusion, in order to address the remaining questions pertaining to brain anatomy in Angelman syndrome, with specific regard to myelination, hydrocephalus, gyration and cerebellar organisation, comprehensive studies using currently available techniques must be conducted. For studying myelination in infants below 9 months of age, we suggest using inversion recovery sequences. The advent of recent MRI techniques may greatly contribute to this field. For example, diffusion tensor imaging tractography may provide valuable insights in the organisation of association fibres between different cortical areas. Functional MRI and other
functional imaging techniques may contribute to the understanding of important aspects of the phenotype. Technical difficulties relating to patient’s cooperation may be overcome by using certain paradigms as for some electrophysiological studies or in the study of sleep. Finally, we want to stress that histological study of brain tissue is also still important for addressing the neurology of Angelman syndrome. Among the merits of Harting and colleagues’ contribution, their report highlights the need to question oft-repeated but yet unverified notions.

REFERENCES


