

'Puppet' children. A report on three cases (1965)

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Angelman H. 'Puppet' children. A report on three cases. *Dev Med Child Neurol* 1965; 7: 681–88.

The association of mental retardation with abnormal physical development of congenital origin still includes a great variety of conditions whose causation is undetermined and which lack precise classification. The (three) children described here possess such similarities as to justify combining them into a specific group, as yet of unknown cause. Their flat heads, jerky movements, protruding tongues and bouts of laughter give them a superficial resemblance to puppets, an unscientific name but one which may provide for easy identification.

It will be seen that all these children possess a number of characteristic features in common and may be summarised as follows:

1. A horizontal depression in the occipital region of the skull, present at birth. Also brachycephaly associated with microcephaly, becoming more obvious as growth proceeds, but not due to premature fusion of the coronal sutures.
2. A varying degree of primary optic atrophy, associated with incomplete development of the choroid.
3. Abnormal air encephalograms indicating some degree of cerebral atrophy associated with ventricular dilatation.
4. Very frequent fits resembling a hypsarrhythmic state and a profound degree of mental retardation.
5. Easily provoked and prolonged paroxysms of laughter.
6. Ataxia, with weakness of the limbs and trunk resembling that seen in cerebellar deficiency.
7. Ability to protrude the tongue to an unusual degree.

Commentary

This seminal article by Harry Angelman is the first description of the syndrome he termed 'puppet children', which later became known as happy puppet syndrome and then Angelman syndrome. The astute observation that the three children described shared a number of physical and behavioural features is remarkable considering the rarity of the condition which has a prevalence of between 1 in 12 000 and 1 in 40 000 and that in the subsequent 10 years only a further 14 cases were reported. Angelman syndrome has since captivated attention as an important model for the notion of behavioural phenotypes and for the influences of genomic imprinting and epigenetic modification of the human genome.

Along with Lesch-Nyhan syndrome in 1964 this account is one of the earliest reports of a 'behavioural phenotype'. It is

striking that the children reported in this paper all had a severe form of the condition whereas more recently milder phenotypes have been identified. Other behavioural features have been since added to the picture, including hyperactivity, stereotypies, and sleep disturbance. Severe speech impairment is a cardinal feature of the syndrome although some children may gain a few words and many enjoy gestural forms of communication. Intriguingly, the happy disposition and uncontrolled laughter thought to be a core feature of the condition has been questioned in a recent case-control study¹ which found a similar pattern of behaviour in individuals with intellectual disability. Likewise, the hand-flapping stereotypies may also be seen in many children with other developmental disorders. Nevertheless, the behavioural symptoms, together with the distinctive physical features constitute a convincing phenotype which has stimulated the quest for genetic diagnosis.

Angelman syndrome and its counterpart Prader-Willi syndrome are one of the earliest described examples of genomic imprinting, a process that determines differential expression of genes according to maternal or paternal origin. The genetic defect responsible for Angelman syndrome is on chromosome 15 inherited from the mother, whereas that responsible for Prader-Willi syndrome is on chromosome 15 inherited from the father. Angelman syndrome is caused by deficient expression of the imprinted *UBE3A* gene. In the normal brain, the maternal copy of the gene performs most of the *UBE3A* functions. This gene encodes the ubiquitin-protein ligase E3A which has a role in protein catabolism and may also be linked to glutamergic neurotransmission. The most common defect, in 70%, is deletion of 15q 11-q13 and children with this defect typically have a more marked phenotype with more severe intellectual impairment and epilepsy. But Dan asserts¹ 'although the *UBE3A* gene is the only factor needed to cause Angelman syndrome its role in the syndrome's manifestations is a matter for speculation'.

Typically, the condition is not diagnosed until late infancy when developmental delay and seizures cause concern. Earlier on, the manifestations may be subtle and perhaps the engaging disposition of the children belies the underlying neurological deficit. Just as in Dr Angelman's day, as Williams points out, 'the diagnosis of the condition is (still) primarily a clinical one'.¹ A sharply observant, intuitive clinician who recognizes the characteristic picture holds the key to the child's future.

Hilary Hart

Reference

1. Dan B. Angelman Syndrome. *Clinics in Developmental Medicine* No. 177. London: Mac Keith Press, 2008.