American Journal of Medical Genetics 122A:155–158 (2003)

Clinical Report

Retinochoroidal Atrophy in Two Adult Patients With Angelman Syndrome

A. Rufa,[1] M.T. Dotti,[1] A. Orrico,[2] C. Battisti,[1] F. Carletto,[3] and A. Federico[1]*

[1]*Unit of Neurometabolic Disease and Research Centre for Diagnosis, Therapy and Prevention of Neurohandicap, Department of Neurological and Behavioural Science University of Siena, Italy*
[2]*Unit of Medical Genetics, Azienda Ospedaliera Senese, Siena, Italy*
[3]*Associazione "Anni Verdi", Rome, Italy*

We describe a new ocular finding, retinochoroidal atrophy (RCA), associated with optic disk paleness in two adult patients with Angelman syndrome (AS) due to maternal 15q11-13 deletion. The ocular involvement described in children with AS consists iris and choroids hypopigmentation due to loss of function of one copy of *P* gene involved in maternal deletion. The loss of one copy of the same gene of paternal origin leads to a similar ocular phenotype as in Prader–Willi syndrome (PWS). However to our knowledge, RCA has never been described before in PWS, suggesting that other maternally expressed genes, particularly *UBE3A*, could be responsible for the retinal changes observed in the adult AS phenotype. Although, further investigations would be necessary to better understand the role of the UBE3A in the retina, the findings reported here should prompt a systematic ophthalmologic evaluation adult patients with AS in order to establish the real incidence of RCA and prevent further disability in these patients.

KEY WORDS: Angelman syndrome; adult phenotype; retinochoroidal atrophy

INTRODUTION

Angelman syndrome (AS) (MIM no. 105830) is a genetic disorder characterized by neurodevelopmental delay with severe intellectual disability, speech absence, inappropriate laughter, sleep disturbances, movement disorders, gait ataxia, seizures, and characteristic electroencephalographic pattern [Angelman, 1965]. Frequently associated features include postnatal microcephaly, macrostomia with wide-spaced teeth and tongue thrusting, prognathia, strabismus, hypopigmentation of hair, skin, and eyes [Scheffer et al., 1990; Clayton-Smith and Pembrey, 1992; Clayton-Smith, 1993]. Genetically, AS results from the loss of function of maternally-expressed genes clustered on chromosome 15q11-q13 and subject to genomic imprinting [Laan et al., 1999]. The most common defect (60–75%) arises from a large maternal deletion, whereas point mutations involving UBE3A, abnormalities in the imprinting processes and paternal uniparental disomy (UPD) have been reported in a minority of patients. In 10–15% of patients with a clinical diagnosis of AS, identifiable molecular abnormalities have not been shown [Malcolm et al., 1991; Nicholls et al., 1998; Jiang et al., 1998b].

The complete clinical picture is associated with maternal 15q11-13 deletion (contiguous gene syndrome) [Beuten et al., 1993; Smith et al., 1996]. Consensus clinical diagnostic criteria for AS have been developed to aid in the clinical recognition of patients who could benefit from molecular investigations [Williams et al., 1995]. Nevertheless, diagnosis can be difficult in adulthood as the clinical findings differ from those described in childhood and other manifestations, such as kyphosis, ocular abnormalities, "velvet like skin" and coarse face, may become more pronounced in older patients [Sandanam et al., 1997; Buckley et al., 1998].

Ocular involvement in AS includes iris and choroids hypopigmentation, strabismus, macular hypoplasia, nystagmus, and abnormal routing of visual pathways [Thompson et al., 1999]. Involvement of the *P* gene in the 15q11-13 region is known to be responsible for oculocutaneous hypopigmentation in patients with deletion [Rinchik et al., 1993]. Most ocular findings have been

*Correspondence to: Prof. Antonio Federico, Research Centre for Diagnosis, Prevention and Therapy of Neurohandicap, University of Siena, Viale Bracci, 53100 Siena, Italy.
E-mail: federico@unisi.it

Received 17 May 2002; Accepted 13 February 2003
DOI 10.1002/ajmg.a.20217