Visual evoked potentials in Prader-Willi syndrome

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Abstract. Oculocutaneous, electrophysiological, and cytogenetic factors were evaluated in 14 patients with Prader-Willi syndrome and in three controls, two albinos and a normal observer. In a substantial number of PW patients chromosomal anomalies, particularly deletions of the long arm of chromosome 15 as well as hypopigmentation of hair, skin, and eye have been identified. In the genetic condition of albinism, hypopigmentation related to neural ectoderm derivatives is associated with reduced visual acuity, foveal hypoplasia, and aberrant retinogeniculocortical projections. The latter can be observed by visual evoked potential (VEP) assessment of hemispheric response symmetry. To determine the possible neural ectodermal origin of hypopigmentation and its involvement in ocular development and optic pathway integrity, the potential distributions of the pattern onset/offset VEP were examined. Our results show hypopigmentation in 13 of our 14 PW patients and a chromosome abnormality in 6; no correlation between these two features was found. None of the PW patients showed the characteristic contralateral hemispheric asymmetry seen in albinism. On the other hand their VEP profiles were found to be atypical, rendering waveform and cortical topography difficult to interpret. Analysis suggests that in the absence of VEP evidence for optic pathway misprojection, PW hypopigmentation is probably of neural crest origin.

Introduction

Hypopigmentation associated with neural ectoderm derivatives, including the retinal epithelium and optic stalk, results in severe structural and functional visual system deficits [1, 2]. We now know that melanin-bearing cells in the developing retina and optic stalk regulate the patterns of axonal growth and pathfinding [3]. Interruption of the normal histogenesis of these two neural ectoderm derivatives due to pigment cell anomalies results in a sequela of visual pathway anomalies including foveal hypoplasia and dramatic retinal fiber misprojections [4, 5]. The anomalous retinofugal projections take the form of temporal retinal fibers which erroneously decussate at the optic chiasm, disrupting retinotopic organization throughout the pathway [6, 7].
A highly sensitive test of the condition of misrouted optic pathway projections is the visual evoked potential (VEP) examination of the potential distribution across the occiput following full-field monocular stimulation of typically an appearing/disappearing checkerboard pattern [8]. The electrophysiological signature of misrouted retinofugal projections is contralateral hemispheric response lateralization of an early VEP component in the pattern onset response. That is, following full-field right eye stimulation, the evoked potential activity lateralizes to the left hemisphere, whereas left eye stimulation results in right hemispheric response lateralization.

This specific form of VEP asymmetry was presumed pathognomonic to albinism [9]. Recently, however, several reports suggest that some patients with a multisystem congenital syndrome called Prader-Willi (PW) demonstrate the presence of misrouted optic pathway projections [10, 11]. The major obligate features of PW include infantile hypotonicity, hypogonadism, hyperphagia with childhood obesity, and mental retardation (for review, see reference 12). Secondary features include small hands and feet, short stature, skeletal anomalies, small bifrontal diameter, and strabismus. In the last few years pigmentation and chromosomal disorders have also been added to the list of secondary features [13–16]. Pigment anomalies now include hypopigmentation, more specifically iris diaphany and fair hair and skin. Chromosome changes include a small deletion of the proximal long arm of chromosome 15 (15q11–q12). Some authors further purport a correlation between hypopigmentation and the chromosome 15q deletions [11].

These recent reports immediately suggest that if misrouting is indeed present in some PW patients, particularly those with hypopigmentation and/or chromosome 15q deletion, then this genotype may also effect neural ectoderm anomalies. To test this hypothesis, we examined 14 unselected patients clinically diagnosed with PW. By random sample, our PW patients included individuals 1) with and without chromosome 15 deletion and hypopigmented hair and/or skin, and 2) with and without chromosome 15 deletion with dark hair and/or normally pigmented skin.

Our electrophysiological results do not support the neural ectoderm hypothesis, for regardless of the presence or absence of hypopigmentation, chromosomal anomalies and/or ophthalmic symptoms including strabismus, reduced acuity, and foveal hypoplasia, none of our sample of PW patients showed any evidence of optic pathway misprojections. We did, however, find a curious VEP response profile which may have been mistaken by previous authors as an electrophysiological sign of misrouting.