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Value of electrodiagnostic assessment in nonsyndromic microcephaly

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PURPOSE. *To evaluate the value of electroretinogram (ERG) and visual evoked potentials (VEP) in children with nonsyndromic microcephaly.*

METHODS. *In this observational case series, six children with nonsyndromic microcephaly aged 8.5 to 158 months were examined. Main outcome measures included the amplitude of the flash ERG (photopic, flickering, scotopic, and dark-adapted responses), the amplitude and latency of the VEP (flash or pattern-reversal stimulus), visual acuity, slit-lamp biomicroscopy, and indirect ophthalmoscopy.*

RESULTS. *Three children demonstrated normal fundus appearances, ERG, and VEP responses: two in this group demonstrated poor vision and brain computed tomography in the third showed schizencephaly. The remaining three children demonstrated abnormal ERG with predominant reduction in photopic amplitudes. Retinal pigmentary granularities were detected in two children in this group, one of whom has poor vision, generalized brain atrophy, and 40% reduction in VEP amplitudes.*

CONCLUSIONS. *Abnormal ERG is not uncommon among children with nonsyndromic microcephaly. Although cone photoreceptors are affected more than rods, this does not anticipate poor vision. It appears that defects in posterior visual pathway or developmental malformations of the brain should be responsible for poor visual function in nonsyndromic microcephaly. (Eur J Ophthalmol 2003; 13: 702-9)*

KEY WORDS. *Microcephaly, Electroretinogram, Visual evoked potentials*

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INTRODUCTION

Microcephaly is a rare condition in which the occipito-frontal head circumference is more than 2 standard deviations below the average for age, sex, race, and gestation. The condition may present at birth (congenital) or a few years afterward. Microcephaly can be categorized into three groups, including primary or true microcephaly, secondary microcephaly, and syndromic microcephaly. Developmental malformations of brain growth result in primary microcephaly. Children with secondary microcephaly may have a history of intrauterine infection or hypoxic injury during the perinatal or postnatal period. Microcephaly also can be associated with many syndromes or chromosomal abnormalities such as Prader-Willi syndrome, Smith-Lemli-Opitz syndrome, trisomy 13, and trisomy 18 (1-4).

Ocular abnormalities that have been described in patients with nonsyndromic microcephaly include strabismus, optic atrophy, congenital hypertrophy of the retinal pigment epithelium, and chorioretinal dysplasia (5-8).

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Microcephaly with chorioretinopathy is a disorder in which children with microcephaly demonstrate abnormal photoreceptor functions with or without structural changes of the retina. Previous reports showed involvement in both rods and cones (9, 10). The condition may be inherited autosomal dominant or recessive. In this study, we determined the patterns of the electroretinogram (ERG) and visual evoked potentials (VEP) and the prognosis for visual function in six children with nonsyndromic microcephaly.

METHODS

This is an observation case series performed at the Department of Ophthalmology, Siriraj Hospital Mahidol University, Bangkok, Thailand. Six consecutive children who were diagnosed with nonsyndromic microcephaly at various ages were referred for ophthalmic evaluation between May 2000 and July 2001. The pediatricians caring for the patients suspected ocular problems in all except Patient 3. All patients were male with no family history of microcephaly, mental retardation, or eye diseases. Pregnancy and birth history were normal except for Patient 5, who had a history of birth asphyxia. All were born full term with two normal labors, three caesarian sections, and one forceps extraction. Investigations for intrauterine infections were negative.

Age at ophthalmic evaluation ranged from 8.5 to 158 months. Main outcome measures included the amplitude of the flash ERG, the amplitude and latency of the VEP (flash or pattern-reversal stimulus), the assessment of vision, slit-lamp biomicroscopy, and indirect ophthalmoscopy. Goldmann perimetry could be performed only in Patient 3. Electrodiagnostic assessment was performed under oral chloral hydrate sedation (50 mg/kg) in all patients except for Patient 3, in whom sedation was unnecessary. VEP examination was performed before the ERG evaluation. All except Patient 3 had flash VEP with stimulus intensity 16 (6.6 candela seconds/m^2). Patient 3 had pattern-reversal VEP with checkerboard stimulus size 2 (16 checks horizontally with width of 23 mm and angle 40 minutes at eyes). The stimulus patterns of the flash ERG were composed of photopic white, photopic red, flickering white, scotopic blue, and dark-adapted white stimuli. The protocol for ERG examination was as follows: dilate pupil with 1% tropicamide eye drops; apply neutral, reference, and active skin electrodes; record baseline activity to check connections and ensure patient is relaxed; record 2-Hz frequency photopic responses under room lighting using white and red stimuli with flash intensity 16; record 30-Hz flicker responses using white stimulus with flash intensity 8; reduce stimulus intensity to 1 and switch off room lighting for 30 minutes; record 2-Hz frequency scotopic responses using blue stimulus; record dark-adapted bright light response by using white stimulus with flash intensity 16. Generally, 100 cycles are averaged depending on the technical quality of the recordings. Each trial was repeated two to three times to verify reliability and the measurements were made from the grand averages of the individual trials. Patient 5 was previously evaluated by ERG and VEP at the age of 9 months. The results were compared to the recent study at 51 months in order to evaluate progression of the condition.

RESULTS

Table I summarizes the general information of the patients. Most of them were diagnosed with microcephaly before 2 years of age. In Patient 3, the diagnosis was delayed until age 12. Of the two patients whose head circumference was recorded at birth (4 and 6), both demonstrated congenital microcephaly.

Four patients demonstrated mild dysmorphic facial features including synophrys, long philtrum, and malformed or prominent ear pinna. Two patients (1 and 4) had some degree of hypotonia and one patient (5) had spasticity. Mental retardation varied from mild to profound. Computerized tomography of the brain revealed alteration of brain structures in two patients. One demonstrated a closed lip schizencephaly (Patient 1) and the other generalized brain atrophy (Patient 5). Chromosome analysis was performed only in Patient 1, and the results were normal.

Table II summarizes the details of the ophthalmic evaluation. Visual acuity could be assessed with Snellen vision chart in only one patient (3). Three patients demonstrated poor fix and follow vision (Patients 1, 2, and 5). None demonstrated nystagmus. Strabismus was observed in half of the patients (4, 5, and 6). All demonstrated intermittent exotropia. Slit-lamp biomi-

TABLE I - GENERAL INFORMATION ON THE PATIENTS

Characteristics	Patient no. 1	2	3	4	5	6
Birth weight (g)	3340	2900	2020	3850	3740	2350
HC at birth (cm)	NA	NA	NA	34	NA	31
Age at diagnosis (mo)	18	6	146	12	8	Diagnosed at birth
HC at diagnosis (cm)	41	37.5	45	42.5	40	31
Dysmorphic features	Mild	None	Mild	Mild	None	Mild
Mental retardation	Moderate	NA	Mild	Moderate	Profound	NA
Brain CT	Closed lip schizencephaly	NA	Normal	Normal	Generalized brain atrophy	Normal
Chromosome analysis	46, XY	NA	NA	NA	NA	NA

All patients were male
HC = Head circumference; NA = Not available; CT = Computed tomography

TABLE II - DETAILS OF OPHTHALMIC FINDINGS

Characteristics	Patient no. 1	2	3	4	5	6
Age at examination (mo)	24	8.5	158	14.5	51	13
VA						
Right eye	Poor F&F	Poor F&F	6/9		Poor F&F	Good F&F
Left eye	Poor F&F	Poor F&F	6/9	Good F&F	Poor F&F	Good F&F
Strabismus	Normal	Normal	Normal	X(T)	X(T)	X(T)
Fundus	Normal	Normal	Pigmentary granularity	Normal	Pigmentary granularity	Normal
VF	NA	NA	Generalized constriction	NA	NA	NA
Refraction						
Right eye	NA	NA	NA	NA	-1 -1.5 x 180	NA
Left eye					-1.00 sphere	
ERG	Normal	Normal	Abnormal	Normal	Abnormal	Abnormal
VEP	Normal	Normal	Normal	Normal	Abnormal	Normal

VA = Visual acuity; F&F = Fix and follow vision; X(T) = Intermittent exotropia; NA = Not available; ERG = Electroretinogram; VEP = Visual evoked potentials

croscopy revealed normal anterior segment of the eye in all patients. Abnormal fundus appearances were observed in two patients (3 and 5). Both showed retinal pigmentary granularities in the midperiphery. Patient 5 also demonstrated a pale optic nerve head. Goldmann perimetry could be performed only in Patient 3. The results showed mild generalized constriction of the visual field tested with different-sized targets in both eyes.

Tables III and IV summarize the ERG and VEP responses compared to a normal 10-year-old subject. Only three patients had abnormal ERG results (3, 5, and 6). Figure 1 demonstrates the ERG recordings in Patient 3 compared to a normal ERG recording of a 10-year-old subject.

Table V summarizes the ERG and VEP of Patient 5 at age 9 and 51 months compared to a normal 10-year-old subject.

TABLE III -SUMMARY OF ELECTRORETINOGRAM (ERG) AMPLITUDES (MV) OF PATIENTS 3, 5, AND 6 COMPARED TO THOSE OF A NORMAL 10-YEAR-OLD SUBJECT

ERG	Patient 3	Patient 5	Patient 6	Normal
Photopic (white flash)				
Right a wave/b wave	18.74/**15.42**	**7.81/21.87**	13.66/**19.91**	14/31
Left a wave/b wave	18.16/**14.14**	**8.20/18.35**	22.25/**23.81**	14/31
Photopic (red flash)				
Right a wave/b wave	**6.05/12.11**	**4.68/12.49**	9.76/**13.27**	10/28
Left a wave/b wave	**5.85/13.46**	**6.64/11.71**	13.28/**16.01**	10/28
Flickering (white flash)				
Right b wave	**13.47**	**18.74**	**11.01**	27
Left b wave	**15.42**	**14.83**	**17.90**	27
Scotopic (blue flash)				
Right b wave	**29.24**	37.50	**23.43**	38
Left b wave	**28.12**	39.84	**32.41**	38
Dark-adapted (white flash)				
Right a wave/b wave	54.37/**78.12**	**46.87/87.49**	51.80/**72.30**	58/115
Left a wave/b wave	62.39/**78.02**	**34.37/84.37**	71.87/**87.49**	58/115

Subnormal results are marked in bold type

TABLE IV - SUMMARY OF VISUAL EVOKED POTENTIAL (VEP) AMPLITUDES (MV) AND LATENCIES (MSEC) OF PATIENTS 3, 5, AND 6 COMPARED TO THOSE OF A NORMAL 10-YEAR-OLD SUBJECT

VEP	Patient 3	Patient 5	Patient 6	Normal (flash)	Normal (pattern-reversal)
Amplitude					
Right eye	9.17	**6.24**	18.35	>10	>5
Left eye	11.32	**5.86**	19.52	>10	>5
Latency					
Right eye	96	127	121	120	100
Left eye	98	123	115	120	100

Subnormal results are marked in bold type

DISCUSSION

All our patients represent nonsyndromic microcephaly. Five of them can be categorized into primary or true microcephaly. Only Patient 5 with a history of perinatal asphyxia may have secondary microcephaly.

A previous report on the ERG responses in microcephaly with chorioretinopathy showed moderately to severely subnormal responses of both rods and cones (9). In microcephaly as part of a syndrome, however, the reported ERG were normal or borderline normal (11). In this study, the ERG results indicate impairment of retinal photoreceptor functions in half of the patients. In addition, all affected patients demonstrate predominant reduction of cone function more than rod function. To our knowledge, this unique finding has not been emphasized in previous reports.

Two of the three patients with abnormal ERG results (3 and 5) demonstrate retinal pigmentary granularities. This is the only abnormal retinal appearance observed in our patients. Other retinal abnormalities that have been reported in the literature include lacunar depigmentation, pigment clumping and bone spicules, bull's-eye maculopathy, choroidal and retinal atrophy, and congenital hypertrophy of the retinal pigment epithelium (6, 9).

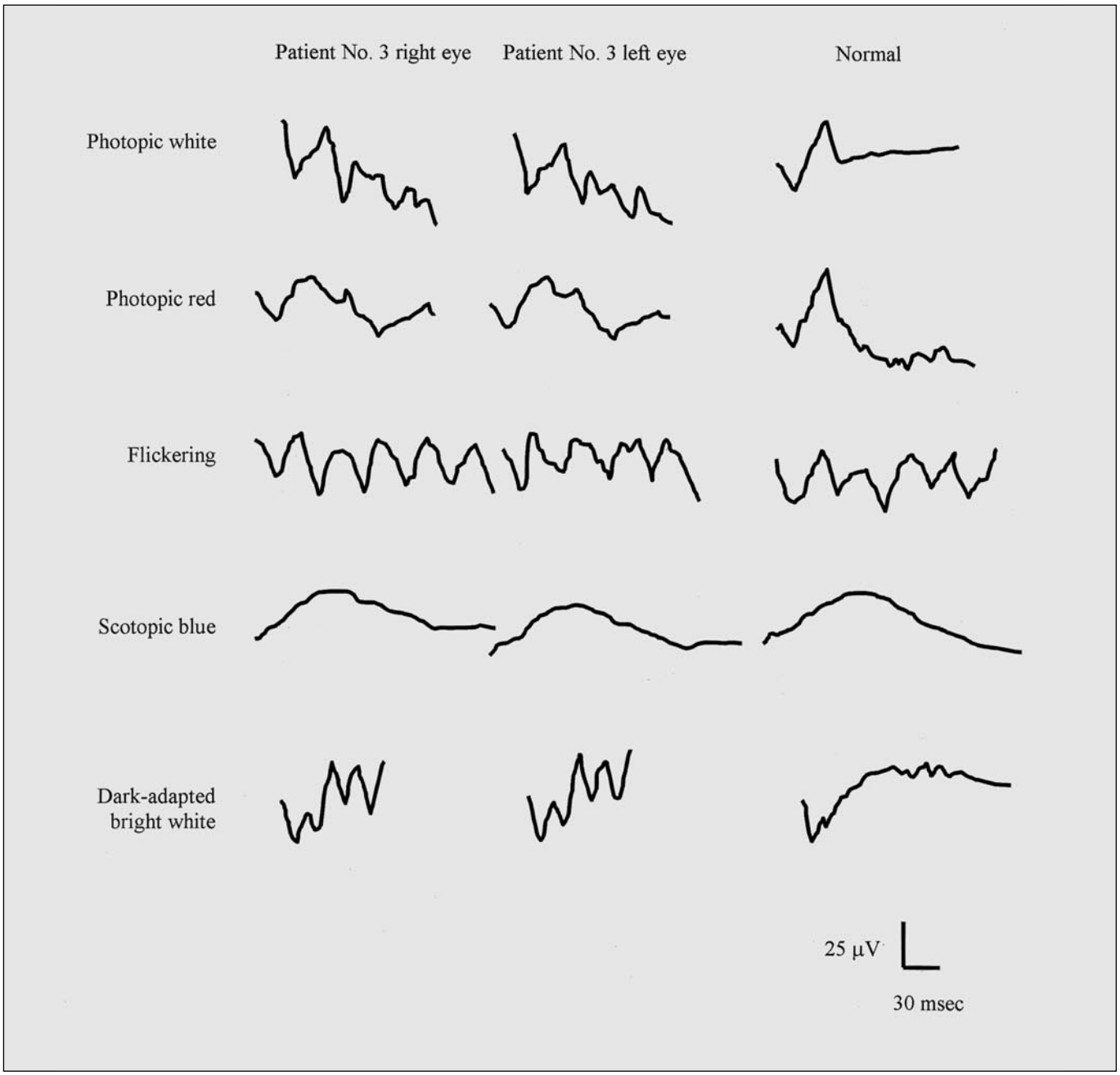

Fig. 1 - *Electroretinogram of Patient 3 compared to that of a normal 10-year-old subject.*

Despite the impairment of cone photoreceptor function, two of the three patients with abnormal ERG demonstrate good vision. In contrast, two of the three patients with normal ERG demonstrate poor vision. This implies that the ERG does not predict visual function in nonsyndromic microcephalic patients.

Patient 5 demonstrates poor fix and follow vision. This patient is an example of secondary microcephaly; i.e., an insult during the perinatal period caused generalized brain damage followed by abnormal growth of the brain. Although there are similarities between this patient and Patient 3 in terms of fundus

TABLE V - PATIENT 5: ELECTRORETINOGRAM (ERG) AMPLITUDES (MV) AND VISUAL EVOKED POTENTIALS (VEP) (MV) AND LATENCIES (MSEC) AT AGE 9 AND 51 MONTHS COMPARED TO THOSE OF A NORMAL 10-YEAR-OLD SUBJECT

ERG or VEP	Age 9 months	Age 51 months	Normal
ERG			
Photopic (white flash)			
Right a wave/b wave	**9.37/14.84**	**7.81/21.87**	14/31
Left a wave/b wave	**12.89/15.62**	**8.20/18.35**	14/31
Photopic (red flash)			
Right a wave/b wave	**8.59/16.40**	**4.68/12.49**	10/28
Left a wave/b wave	**6.64/13.28**	**6.64/11.71**	10/28
Flickering (white flash)			
Right b wave	**15.65**	**18.74**	27
Left b wave	**15.62**	**14.83**	27
Scotopic (blue flash)			
Right b wave	**10.93**	37.50	38
Left b wave	**10.35**	39.84	38
Dark-adapted (white flash)			
Right a wave/b wave	**24.99/46.87**	**46.87/87.49**	58/115
Left a wave/b wave	**37.50/56.25**	**34.37/84.37**	58/115
VEP			
Amplitude			
Right eye	**3.31**	**6.24**	>10
Left eye	**3.32**	**5.86**	>10
Latency			
Right eye	119	127	120
Left eye	120	123	120

Subnormal results are marked in bold type

changes and abnormal ERG responses, their visual acuity is different. Patient 3 has normal vision; Patient 5 shows poor fix and follow vision. An obvious difference between these two patients is the VEP response; Patient 3 shows normal response and Patient 5 shows moderately decreased VEP amplitude. This finding together with the absence of nystagmus indicates cortical visual impairment, which could explain poor visual function in Patient 5. Patients 1 and 2 also demonstrate poor vision. Both have normal ERG and VEP. Patient 1 has severe developmental malformation of the brain that might lead to visual inattention. We do not have the information on the brain computed tomography scan of Patient 2; therefore, the cause of poor vision in this patient remains unclear.

Because none of our patients demonstrates nystagmus, we might infer from this study that the defects in posterior visual pathway or developmental malformations of the brain should be responsible for poor visual function in nonsyndromic microcephaly.

Different types of strabismus can be associated with syndromic and nonsyndromic microcephaly. Intermittent exotropia was the only type of strabismus seen in our patients. Slight myopic shift was demonstrated in one patient of this group. We did not observe significant amblyopia except in Patient 5, who developed poor vision in both eyes due to brain pathology.

Manning et al reported a follow-up ERG in a patient with microcephaly and inferior chorioretinal degeneration (10). They found no change in the ERG results over the 14-year interval. We had the opportunity to compare the ERG and VEP responses of Patient 5 between ages 9 and 51 months. This 42-month follow-up shows marked improvement in scotopic b wave responses and some improvement in the dark-adapt-

ed b wave responses as well as the amplitudes of the VEP responses in both eyes. The VEP responses indicate either incomplete recovery of cortical visual impairment or delayed visual maturation.

Microcephaly can be associated with several malformations of brain development: for example, lissencephaly, pachygyria, and schizencephaly (9, 12, 13). One of our patients (Patient 1) demonstrated a closed lip schizencephaly, which is a rare developmental disorder characterized by abnormal cleft in the cerebral hemisphere. This patient also had moderate global developmental delay and mild dysmorphic facial features. Vargas et al compared the prevalence of major and minor anomalies in infants with congenital microcephaly with that among normocephalic infants (14). They concluded that microcephalic infants did not have a higher frequency of minor anomalies and major anomalies were also rare. They found a higher frequency of frontal bossing, small chin, and short nose with anteverted nares, which was associated with small body size rather than microcephaly. We found dysmorphic facial features in four patients. All were minor anomalies such as synophrys, long philtrum, and malformed ear pinna. There were no explicit facial features observed in our group of patients.

Primary microcephaly can be inherited either as an autosomal recessive or dominant trait. Recently, molecular genetics of human microcephaly have been studied aggressively and several loci responsible for microcephaly have been mapped (15). Furthermore, microcephaly has been observed in several chromosomal disorders and syndromes including an inborn error of metabolism (16, 17). This indicates etiologic heterogeneity of microcephaly.

Besides the studies in molecular genetics of microcephaly, environmental factors have also been investigated as a possible origin of microcephaly (18). The results suggest some preventive effect of folic acid and iron against isolated primary microcephaly.

Although there is no specific treatment for microcephaly, the clinicians caring for affected children should be aware of the possibility of visual problems and provide appropriate support to improve their visual function.

In conclusion, although abnormal cone function is common among children with nonsyndromic microcephaly, it is not directly related to loss of central vision. Rather, defects in posterior visual pathway or developmental malformations of the brain are responsible for poor visual function in this group of patients.

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