

**Chapter 2**

The key role of electrophysiology in the diagnosis of visually impaired children.

van Genderen MM<sup>1</sup>, Riemslag FCC<sup>1</sup>, Jorritsma FF<sup>1</sup>,  
Hoeben FP<sup>1</sup>, Meire FM<sup>2</sup>, Stilma JS<sup>3</sup>

*Accepted for publication in Acta Ophthalmologica Scandinavica*

<sup>1</sup> Bartiméus Institute for the Visually Impaired, Zeist, The Netherlands

<sup>2</sup> University Children's Hospital Koningin Fabiola, Brussel en University Hospital Gent, Belgium

<sup>3</sup> Department of Ophthalmology, University Medical Centre Utrecht, The Netherlands



## ***The key role of electrophysiology in the diagnosis of visually impaired children***

### **Abstract**

- Purpose:** To describe the outcome of specialized electrophysiology in visually impaired children.
- Methods:** Retrospective evaluation of 340 electrophysiological examinations performed in 298 children over a three year period (2001-2003), with regard to demographic data, referral pattern, degree of compliance, and diagnostic results. Electrophysiology was performed without sedation or anaesthesia. In ERGs, DTL electrodes were used in combination with on line selection of responses. VEP testing was performed with seven active occipital electrodes.
- Results:** Mean age was  $7 \pm 5$  yrs; 72 (24%) of the children were mentally as well as visually impaired. Main reasons for referral were suspected posterior segment disease, abnormal visual development, unexplained low vision, high myopia, and suspected albinism. Compliance was good in 302/340 (88%), partial in 24/340 (7%), and absent in 14/340 (4%) of the examinations. Of the 326 successful procedures, 215 (66%) showed abnormal results. Tapetoretinal dystrophy (22%), opticopathy (16%), congenital stationary night blindness (13%), and cone dystrophy (11%), were the most frequently established diagnoses. Albinism was confirmed in 14 of 24 suspected patients; additionally, unsuspected misrouting was found in 6. In 26 (9%) of the patients, a previously established diagnosis was changed.
- Conclusions:** In a specialized setting, electrophysiological examinations can successfully be performed in visually impaired children. The results are essential for the final ophthalmological diagnosis and have important consequences for rehabilitation.
- Key words:** ERG, VEP, visually impaired children, childhood blindness, DTL electrodes, misrouting

## **Introduction**

Knowledge of an exact ophthalmological diagnosis is essential in the rehabilitation of a visually impaired child. The diagnosis clarifies the aetiology and consequently the genetics of the disorder, it provides an explanation for various visual problems of the child, and it implies the prognosis. The diagnosis may contribute to decisions about reading print or Braille, or which forms of education or career are feasible.

In several posterior segment disorders visual electrophysiology plays a decisive diagnostic role, because psychophysical testing in infants and young children is limited, and ophthalmological examination may initially reveal a normal looking retina even in the case of severe retinal dystrophy.<sup>1</sup> In older children, funduscopy may be hampered by photophobia or severe nystagmus, or the clinical signs and retinal appearance may fit a number of diagnoses. We report on the outcome of 340 electrophysiological examinations in children from a three year period (2001-2003), performed without anaesthesia or sedation, with the use of specialized recording methods. The outcome parameters were the demographic data of the children, the referral pattern, the compliance with the procedure, the type and result of the electrophysiological examination, and the contribution towards the final diagnosis.

## **Patients and methods**

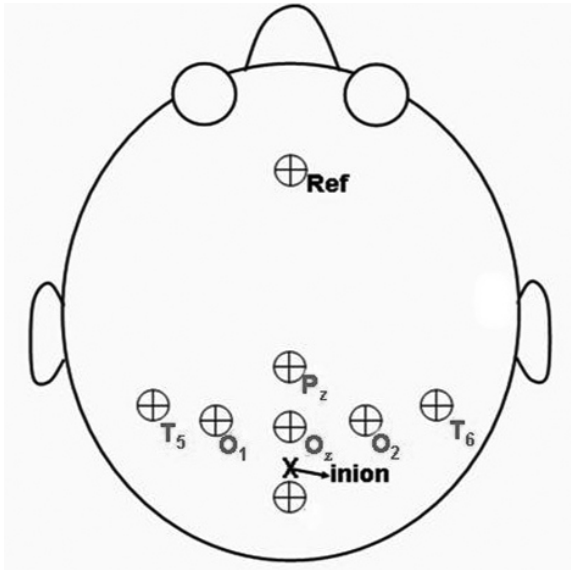
The Bartiméus Institute is one of the Dutch institutes for the rehabilitation of visually impaired people, and the only one with an electrophysiology department. In the years 2001, 2002, and 2003, a total of 357 patients were referred for electrophysiological investigations by ophthalmologists, paediatricians, neurologists and genetic specialists; 298 of these patients were children under 18. The 59 adult patients were mainly family members of visually impaired children, in which electrophysiological results were needed for genetic counselling; the outcome of their examinations will not be discussed in this study.

Information regarding the demographic data of the children, the reasons for referral, and the referring clinicians were obtained from the medical records.

The compliance with the electrophysiological procedure was graded as *good* if a child could undergo a complete protocol, including, in ERGs, the required 20 minutes of dark adaptation. We considered compliance to be *partial* if the procedure had to be shortened, for instance because the child was afraid of the dark.

*Absent* compliance meant the procedure had to be aborted before usable measurements could be made. Compliance was optimized by the following measures. Small children sat on a parent's lap while the electrodes were attached and during the recording. Compliance in infants could sometimes be increased by bottle feeding during the procedure. An assistant was always present in the same room as the parents and child to intervene if something went wrong, to give instructions, and to reassure and distract the child (and the parents). Communication of the investigator with the assistant, parents, and child remained possible because the examination and the recording room were separated only by curtains. Throughout ERG as well as VEP recordings the assistant encouraged the child to fixate on the stimuli; the assistant was guided by feedback from the examiner, who monitored fixation with closed-circuit (infrared) television. During VEP stimulation, the assistant drew the child's attention to the pattern stimulus by moving noisy toys along the upper part of the screen; the assistant could manually halt averaging if fixation was inadequate.

Visual electrophysiology was performed without sedation or anaesthesia. For the ERG, we used DTL (Dawson, Trick, Litzkow)<sup>2</sup> electrodes in all children except for nine infants (< 1 year of age), who were examined with contact lens electrodes. The investigator assessed on line every single flash ERG response, excluding from averaging responses that were unreliable because of inadequate fixation, blinking etc. ERGs were recorded according to ISCEV standards.<sup>3</sup> For the standard ISCEV ERG measurements, Xenon tube flashes (duration ca 10  $\mu$ s) were delivered in a custom made Ganzfeld dome, at one flash every 2 seconds for the low (-2.6 ND), and one flash every 5 seconds for the standard ISCEV intensity (mixed response). Subjects were then light adapted for 10 minutes by exposure to a white 30 cd/m<sup>2</sup> rod saturating background, and photopic ERGs were recorded to standard ISCEV intensity and to white 30 flashes per second. To the standard ISCEV intensities, we added an extended series of stimuli in the dark adapted condition: -2.0, -1.6, -1.0, -0.6, -0.3, and +0.6 log; this extended series provides information about the consistency of the recorded responses. In the light adapted condition we added +0.6 log intensity to the standard ISCEV intensity. In cases of suspected congenital stationary night blindness (CSNB) a "Miyake protocol" was performed: 30 Hz photopic measurements every minute for ten minutes after turning on the background illumination. With this protocol the complete and incomplete forms of CSNB (CSNB1 and 2) can be distinguished.<sup>4</sup>

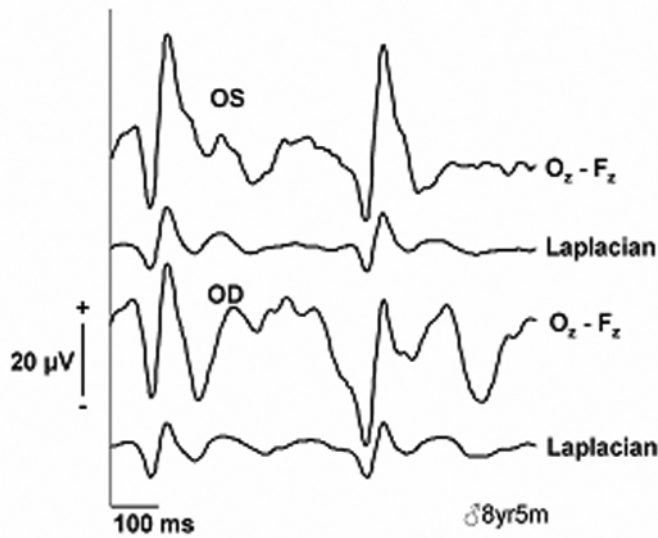


**Figure 1.**

Schematic representation of the position of the electrodes used for VEP. Seven active occipital electrodes are referenced to a frontal midline electrode. The active midline electrode is placed 2 cm above the inion, with two lateral active electrodes on each side, at a spacing of 3 cm. These electrode positions are equivalent to  $T_5$ ,  $O_1$ ,  $O_z$ ,  $O_2$ , and  $T_6$  of the international 10-20 system. Two differential recordings  $O_1 - O_2$  and  $T_5 - T_6$  were calculated. Two vertical active electrodes, also at a spacing of 3 cm, were used for calculation of the Laplacian derivation.

VEP testing was performed with seven active occipital electrodes (see Figure 1). Two differential recordings from active electrodes at both hemispheres enhanced and visualised online the hemispheric differences. Additionally, a Laplacian derivation over the striate cortex amplified the contribution of the striate source relative to the contribution of the extra striate source,<sup>5</sup> which enhances the signal to noise ratio extensively. Responses were recorded to pattern reversal, pattern onset and flash stimulation (flash stimulus energy 1 Joule, duration less than 10 ms; pattern stimulation: VGA monitor, mean luminance 50 cd/m<sup>2</sup>). We used pattern reversal stimulation mainly to detect a possible abnormality of the latency in a patient. (see Figure 2). We assessed misrouting with flash VEPs in infants and toddlers, pattern onset VEPs in older children.<sup>6</sup> Pattern onset VEPs were also used to estimate visual acuity, for instance in preverbal or mentally impaired children, and in children suspected of non-organic visual loss. Check size threshold levels were estimated by presenting the stimuli in a series, in which the larger and smaller checks were presented sequentially and the averaging was carried out over signal segments covering the full series.<sup>7</sup>

Only one EOG was recorded during the three year period, because most disorders with a reduced EOG also show ERG abnormalities that can be recorded at a much younger age. The EOG is essential in the diagnosis of Best's disease, but children



**Figure 2.** Pattern reversal VEP of a normal subject. The positive component (P100) shows remarkably little variation in latency between or within individuals. The normal monocular value for our department is  $107 \pm 3$  ms (N=32).

with this disorder are hardly ever referred to our institute, because the majority does not have significant visual impairment.<sup>8</sup>

All electrophysiological results were judged by a team of clinical physicists and an ophthalmologist. Mean values and standard deviations of normal ERG responses were obtained from 51 subjects (mean age  $10 \pm 4$  yrs) (Table 1). Because of a skewed distribution, mean and standard deviations were calculated after logarithmic transformation.<sup>9</sup> Responses were considered to be abnormal if amplitudes were more than 2SD below the mean, and/or latencies more than 2SD above the mean. VEP latencies were determined from the pattern reversal responses, and considered abnormal if  $\geq 2$  SD above the mean (normal monocular value for our department:  $107 \pm 3$  ms (N=32)).

ERG and VEP responses of infants were interpreted according to guidelines provided in earlier studies.<sup>10-12</sup> The study of Fulton *et al*<sup>10</sup> provided expected limits of normal values of the ISCEV rod, maximal, and cone responses in the first year of life. For instance, a quarter of the normal infants does not have a detectable rod response until 5 weeks of age. In evaluating the responses of infants and young children, we took these maturation effects into account. All diagnoses were recorded before and after the electrophysiological examination.

	stimulus intensity (log to the standard)	a trough to b peak amplitude ( $\mu\text{V}$ )	
		mean	mean - 2 SD
*scotopic	-2.6 ND	143	45
	-2.0 ND	249	98
	-1.6 ND	312	124
	-1.0 ND	394	187
	-0.6 ND	373	193
	-0.3 ND	418	207
*mixed	0.0 ND	481	243
	+0.6 ND	486	253
*photopic	0.0 ND	98	36
	+ 0.6 ND	187	77
*	30 Hz	74	35

**Table 1.** B-wave amplitudes determined in 51 normal subjects, mean age  $10 \pm 4$  years. \*: standard ISCEV ERG measurements.

## Results

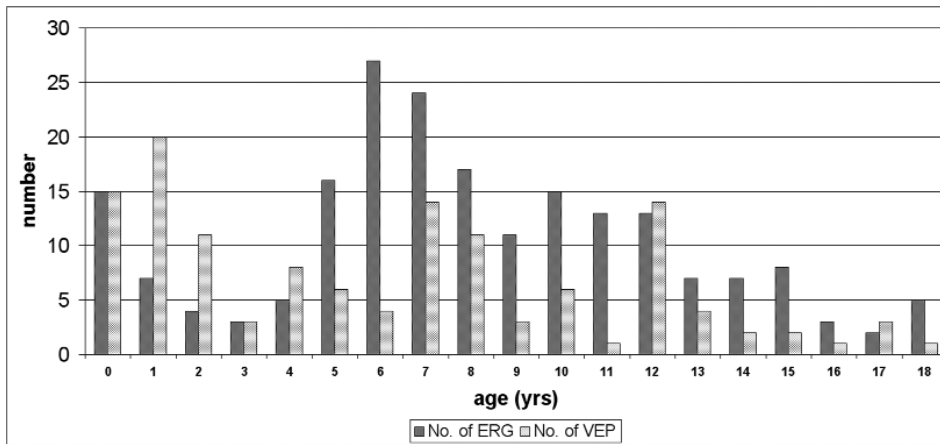
### *Demographic data of the children*

340 examinations were performed in 298 children; 43 children had both an ERG and a VEP. An EOG was measured in only one child. 172 children (58%) were boys, 126 (42%) girls. 72 children (24%) were mentally impaired, and three had hearing loss. Mean age of the children was  $7 \pm 5$  yrs; the age distribution is shown in Figure 3.

51 children (17%) had a visual acuity below 0.05, 156 (53%) between 0.05 and 0.3, or below the normal range for their age.<sup>13,14</sup> 90 children (30%) had a visual acuity of more than 0.3 or within normal range for their age. They were referred because of other visual symptoms, for instance night blindness, photophobia, or high myopia.

### *Referral patterns*

Most electrophysiology referrals came from the Bartiméus ophthalmologists, as part of the diagnostic process and subsequent rehabilitation. Ophthalmologists from other centres for visually impaired children, or from hospitals throughout the country, requested 20% (69/340) of the total number of procedures. In 11 cases, geneticists or paediatricians asked for electrophysiological investigations.



**Figure 3.** The age distribution of the electrophysiologically examined children (N=297, 340 procedures)

The most frequent reason for referral was suspicion of a retinal disorder. In 85 children (90 procedures), this suspicion was based on a combination of symptoms, for instance nystagmus, photophobia, and high hypermetropia. Another 50 children (53 procedures) had one presenting symptom only: either nystagmus, or high myopia, or night blindness. The second largest group (49 procedures) consisted of children with unexplained low visual acuity, or with a visual acuity that could not reliably be determined by psychophysical tests. This group consisted mainly of severely mentally impaired children, and children suspected of non-organic visual loss. Other important reasons for referral were probable albinism, and infants < 1 yr of age with abnormal visual development, for instance, absent fixation and following, or roving eye movements.

#### *Compliance*

Good compliance was achieved in 302/340 procedures (88%). Compliance was partial in 24 (7%) procedures, but in all these cases a diagnosis could be established. Fourteen procedures (4%, 11 ERGs and 3 VEPs) had to be aborted because of non-cooperation; ten involved severely mentally impaired children, the remaining four mentally normal children between one and five years of age. These children had miscellaneous disorders; no diagnosis seemed therefore predominant in the failed procedures. A successful procedure was possible in 62/72 (86%) of mentally impaired children, and 221/226 (98%) of children with normal development.

### *Electrophysiological results*

The results of all successful electrophysiological procedures are summarised in Table 2. The table does not show the one EOG, which was normal, and five procedures that yielded inconclusive results, despite good measurements.

In 82/90 procedures (91%) performed for suspected retinal disease, an electrophysiological diagnosis could be established. Examples of the ERGs in several diagnoses are shown in Figure 4. The most frequently found retinal disorders were progressive tapetoretinal dystrophies (TRD, rod-cone as well as cone-rod dystrophies) (48), CSNB (29), cone dysfunction/dystrophy (24), and achromatopsia (15). Of the patients with CSNB, eight had CSNB1 ("complete" form), fourteen CSNB2 ("incomplete" form), and seven autosomal recessive CSNB. Nine patients with unexplained low visual acuity proved to have non-organic visual loss.

34 procedures were performed in 25 infants; nine infants had both an ERG and a VEP. 35% (12/34) of these procedures yielded abnormal results, VEPs being more often abnormal than ERGs (10 and 2, respectively). 76% (22/29) of children with high myopia as presenting symptom had abnormal electrophysiological findings; cone dystrophy was diagnosed in half of them.

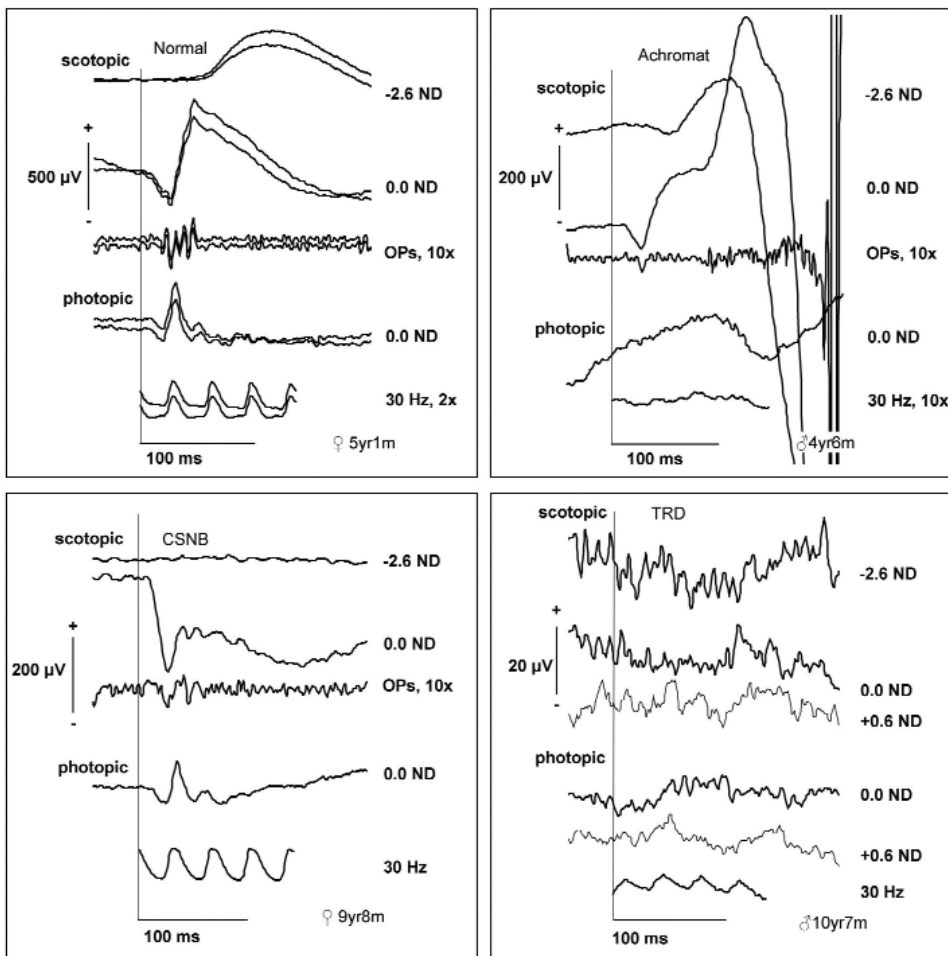
Misrouting was demonstrated in 14 of 24 suspected cases; an example is given in Figure 5. Additionally, misrouting was found in six patients not referred for this diagnosis.

Opticopathy, with or without cerebral visual impairment, was confirmed in 17 of the 21 suspected cases, in 17 patients with miscellaneous symptoms, and in sixteen mentally impaired patients referred for visual acuity assessment.

Three-quarters of the children with abnormal electrophysiological findings had an ophthalmological disorder only, like, for instance CSNB. In the remaining quarter, the electrophysiological diagnosis contributed to the identification of a systemic condition, for example retinal dystrophy as part of a syndrome or metabolic disease.

### *Change of diagnosis*

In 26 patients the electrophysiological results altered a previously assumed diagnosis. In 22 of these cases, the definitive diagnosis considerably changed the prognosis of the condition, for instance CSNB instead of TRD (better prognosis) or TRD instead of X-linked myopia (worse prognosis). (Table 3)

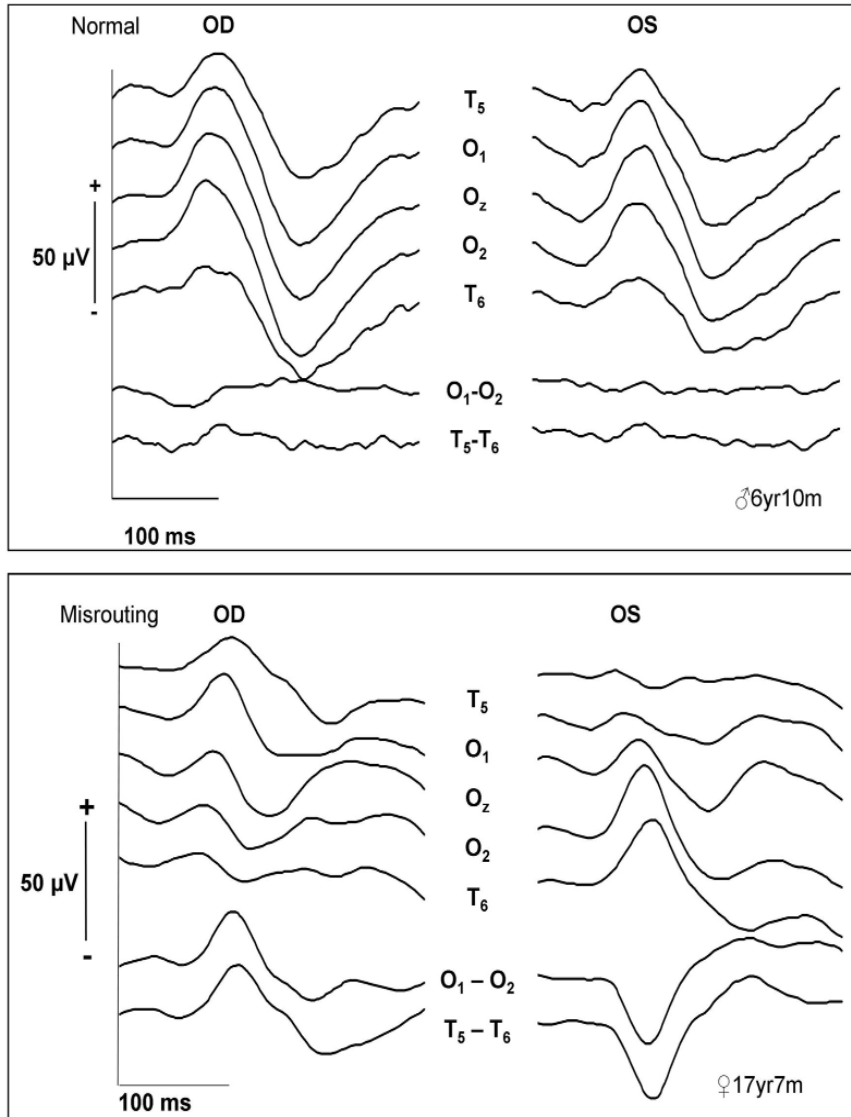


**Figure 4.**

Standard ISCEV ERG responses of a normal subject (top left), a patient with achromatopsia (top right), a patient with CSNB (bottom left), and a patient with retinal dystrophy (bottom right). The diagnoses in the patients were confirmed by DNA analysis.

**Normal subject:** from top to bottom the scotopic responses, mixed response, oscillatory potentials, photopic responses, and photopic response to 30 Hz flicker. **Achromat:** after the scotopic and mixed b-wave, a blink artefact can be seen, probably because of photophobia. Still, based on these recordings the diagnosis could be established. DNA analysis: *CNGB3* mutation<sup>36</sup> **CSNB patient:** the scotopic response is absent, the mixed response shows the characteristic electronegative waveform, the photopic responses are normal. DNA analysis: *GRM6* mutation.<sup>37</sup>

**Retinal dystrophy:** notice the scale difference; there are only very small photopic responses. DNA analysis: *RPE65* mutation.<sup>38</sup>



**Figure 5.**

Responses to pattern onset-offset stimulation of a normal subject (top), and a patient with misrouting (bottom). In the patient with misrouting, the differential recordings O<sub>1</sub>-O<sub>2</sub> and T<sub>5</sub>-T<sub>6</sub> show a positive peak with stimulation of the right eye, which means that the response is found in the left hemisphere. In the left eye, this peak is negative, caused by a response of the right hemisphere.

Reason referral/ presenting symptom ( <i>total no. of procedures</i> )	ERG VEP		ERG		VEP	
	normal		Abnormal		abnormal misrouting	
Suspicion of retinal problem (90)	7	1	TRD 36 CSNB 17 Achr/blue cone 15/3 Cone dystrophy 6 Retinoschisis 1		4*	
Unexplained low vision, visual acuity assessment (49)	21	9	TRD 2		16	1
Infant** (34)	14	8	Cone dystrophy 2		9	1
High myopia (> -6 D) (29)	7		Cone dystrophy 11 CSNB 7 TRD 3			1
Albinism (24)		9			1	14
Opticopathy/CVI (21)		2	TRD 1		17	1
Nystagmus (16)	2	5	Cone dystrophy 5 CSNB 2			2
General syndrome (16)	6	3	TRD 5		2	
Night blindness (8)	3		CSNB 3 TRD 1		1	1
Follow up (25)	1	2		13	9	
Family screening (8)	5	2		1		
<b>Total 320</b>	<b>66</b>	<b>41</b>		<b>134</b>	<b>59</b>	<b>20</b>
	<b>(33%)</b>	<b>(34%)</b>		<b>(67%)</b>	<b>(49%)</b>	<b>(17%)</b>
	<b>Normal</b>		<b>Abnormal</b>			

\* Opticopathy secondary to TRD; \*\* Children <1 yr with abnormal visual development, for instance no fixing or following, roving eye movements, or nystagmus; infants with suspected albinism are counted under "albinism". Abbreviations: Achr: achromatopsia, Blue cone: blue cone monochromacy, CSNB: congenital stationary night blindness, CVI: cerebral visual impairment, TRD: tapetoretinal dystrophy

**Table 2.** Results of electrophysiological measurements (N=320)

original diagnosis	no	p/s*	diagnosis after electrophysiology	no	p/s*
TRD	8	p	CSNB	3	s
			achromatopsia	1	s
			blue cone monochromacy	3	s
			cone dystrophy	1	p
LCA	6	p	optic atrophy/CVI	1	s
			CSNB	3	s
			achromatopsia	1	s
			cone dystrophy	1	p
cone dystrophy	2	p	non-organic visual loss	1	s
			TRD	1	p
CSNB	4	s	myopia	2	s
			cone dystrophy	1	p
			TRD	1	p
X-linked myopia	1	s	TRD	1	p
optic atrophy	1	s	TRD	1	p
non-organic visual loss	1	s	TRD	1	p
					p
congenital nystagmus	1	s	cone dystrophy	1	p
albinism	2	s	congenital nystagmus	1	s
			cone dystrophy	1	p

\*: p: progressive condition; s: stationary condition

Abbreviations: CSNB: congenital stationary night blindness, CVI: cerebral visual impairment, LCA: Leber's congenital amaurosis, TRD: tapetoretinal dystrophy

**Table 3.** Change of diagnosis after electrophysiological examination (N=26)

### **Discussion**

With an electrophysiology department especially adapted for children we were able to establish a diagnosis in 278/298 (94%) of the referred children, without the use of anaesthetics or sedation. The high success rate may partly be attributed to selection of patients. Most children referred for electrophysiology were first examined ophthalmologically, at which time the ophthalmologist could ascertain the probability of sufficient compliance for the procedure. Also we regularly

decided to postpone measuring ERGs in toddlers, unless parents or clinicians had a very urgent reason for knowing the diagnosis. Despite this patient bias and the toddler "dip" in ERGs, as can be seen in Figure 3, more than half of the investigated children were less than eight years of age.

Technical measures to maximize success rate were using an extended stimulus series which made it easier to discern possible trends in the responses, the on-line rejection of unreliable ERG responses, and the use of DTL electrodes. On-line selection of responses was especially advantageous in cases of nystagmus, because nystagmus may make recordings very noisy. DTL electrodes are far more comfortable than contact lens electrodes, have negligible risk of corneal abrasions, and yield much larger amplitudes than skin electrodes.<sup>15</sup> Furthermore, monitoring fixation in a child with DTL electrodes is much easier than with contact lens electrodes. Previous studies describe about 30% lower amplitudes with DTL electrodes compared to contact lens electrodes.<sup>16, 17</sup> However, with selection of responses and fixation monitoring we were able to obtain amplitudes considerably higher than previously described. For instance, we measured a mean (ISCEV standard) mixed response of  $481 \mu\text{V} \pm 119 \text{ mV}$  ( $N=51$ ) (Table 1). This is in the same range as found in adults measured with contact lens electrodes,<sup>10</sup> but in our case in a much younger and less cooperative population.

In VEP testing, fixation was also closely monitored. Furthermore, we used more active occipital electrodes than recommended by ISCEV standards, combined with a Laplacian derivation. Visually (and sometimes also mentally) impaired children frequently have fixation problems or nystagmus.<sup>18, 19</sup> The Laplacian derivation enhanced the signal to noise ratio, while the use of more electrodes increased the chance of a successful recording. An additional advantage proved to be the detection of misrouting in children not suspected of albinism.

Lastly, we tried to optimize compliance by working in a specially equipped environment. The continuous presence of an assistant assured immediate intervention if something went wrong.

Our study depicts an overall picture of diagnoses found in visually impaired children. Previous studies described electrophysiological results of children with one defined abnormality only: for instance children with nystagmus,<sup>20, 21</sup> refractive errors,<sup>22, 23</sup> or cone dysfunction.<sup>24</sup>

Cerebral visual impairment and optic atrophy are the most frequent causes of visual impairment in children in the western world.<sup>25-29</sup> Patients with these disorders were often already diagnosed with cerebral damage by their paediatricians or

child neurologists at the time of referral to our institute. Electrophysiology (VEPs) in these children was therefore mainly used for assessing visual acuity or follow-up. Consequently, the greater part (63%) of procedures in our series consisted of ERGs.

In previous studies on the causes of visual impairment in children, retinal disorders have generally been lumped together.<sup>25, 26, 30-32</sup> In our study, 120 children proved to have a hereditary retinal disorder. Progressive conditions (TRD and cone-dystrophy) occurred in 72/120 (60%), stationary disorders (CSNB, achromatopsia, blue cone monochromacy, and retinoschisis) in 48/120 (40%). The relatively high incidence of CSNB and cone dystrophy may be due to the fact that we examined all highly myopic children that had no obvious reason for their myopia, as, for instance, Down's syndrome. Half of these children had a visual acuity of more than 0.3 (but less than 1.0), and thus were not visually impaired according to the WHO definitions.<sup>33</sup> Quite often their subnormal visual acuity had been contributed to the myopia itself. Previous studies also have stressed the importance of investigating children with high myopia,<sup>22, 23</sup> one study showing that only 8% of children under ten with myopia of more than 6 diopters did not have an underlying ocular or systemic condition.<sup>23</sup>

60% of children with reported night blindness proved to have a retinal disorder. On the other hand, night blindness was not the presenting symptom in the majority of children diagnosed with CSNB. Especially children with CSNB2 ("incomplete" CSNB) often had more problems related to their cone dysfunction, like low visual acuity and photophobia, than problems with night vision.

The electrophysiology results changed a previously established diagnosis in 26 cases. More than half of these cases (14/26) concerned diagnoses of Leber's congenital amaurosis (LCA) or early TRD. These diagnoses had all been electrophysiologically established in infancy or at a very young age, often under anaesthesia. Earlier studies have shown that ERG amplitudes are significantly lower in very young children compared to those in older children,<sup>10, 11</sup> especially the scotopic and maximal responses. Also, several anaesthetics may influence ERG outcomes.<sup>34</sup> Furthermore, some cases of CSNB have been described with initially very low ERG amplitudes, which led to the impression of LCA.<sup>35</sup>

The change of diagnosis had profound implications for the rehabilitation of the children. The approach of a child with non-organic visual loss is very much different from the approach of a child with retinal dystrophy. Several children

thought to suffer from night blindness were shown to have a normal ERG and normal dark adaptation, which made special illumination measures unnecessary. The child that had its diagnosis changed from LCA to achromatopsia was educated to read print instead of Braille.

### ***Conclusion***

In a specialized setting, electrophysiology can reliably be performed in visually impaired children, without anaesthesia or sedation. Because of several technical measures, we were able to obtain considerable ERG amplitudes with DTL electrodes. In VEP testing, using more active electrodes not only increased the chance of a successful recording, but also led to the detection of unsuspected misrouting.

Based on this study, we recommend early referrals in infants (because of the problems associated with performing ERGs in toddlers), children with unexplained high myopia, and night blindness. Rehabilitation of visually impaired children may be directly influenced by electrophysiological results, especially if they lead to a change in diagnosis.

## References

1. Michaelides M, Holder GE, Moore AT. Inherited retinal dystrophies. In: Taylor D, Hoyt CS (ed.) *Pediatric ophthalmology and strabismus*. Elsevier Saunders 2005; Ch 52.
2. Dawson WW, Trick GL, Litzkow CA. Improved electrode for electroretinography. *Invest Ophthalmol Vis Sci* 1979;18:988-91.
3. Marmor MF, Zrenner E. Standard for clinical electroretinography (1994 update). *Documenta Ophthalmol* 1994;89:199-210.
4. Miyake Y, Horiguchi M, Ota I, Shiroyama N. Characteristic ERG-flicker anomaly in incomplete congenital stationary night blindness. *Invest Ophthalmol Vis Sci* 1987;28:1816-1823.
5. Manahilov V, Riemslag FC, Spekreijse H. The Laplacian analysis of the pattern onset response in man. *Electroencephalogr Clin Neurophysiol* 1992;82:220-224.
6. Apkarian P, Reits D, Spekreijse H. Component specificity in albino VEP asymmetry: maturation of the visual pathway anomaly. *Exp Brain Res* 1984;53:285-294.
7. Spekreijse H, Riemslag FCC. Gross potential recording methods in ophthalmology. In: *Vision research*, ed. Carpenter RSH, Robson JG; Oxford University Press 1999:216-233.
8. Ponjavic V, Eksandh L, Andreasson S, Sjostrom K, Bakall B, Ingvast S, Wadelius C, Ehinger B. Clinical expression of Best's vitelliform macular dystrophy in Swedish families with mutations in the bestrophin gene. *Ophthalmic Genet* 1999;20:251-7.
9. Altman DG. Skewed distributions. In: *Practical statistics for medical research*. London, Chapman & Hall 1997: 60-63.
10. Fulton AB, Hansen RM, Westall CA. Development of ERG responses: the ISCEV rod, maximal and cone responses in normal subjects. *Doc Ophthalmol* 2003;107:235-241.
11. Westall CA, Panton CM, Levin AV. Time courses for maturation of electroretinogram responses from infancy to adulthood. *Doc Ophthalmol* 1999;96:355-379.
12. Breceelj J. From immature to mature pattern ERG and VEP. *Doc Ophthalmol* 2003;107:215-224.
13. Teller DY, Morse R, Borton R, Regal D. Visual acuity for vertical and diagonal gratings in human infants. *Vision Res* 1974;14:1433-1439.
14. Salomao SR, Ventura DF. Large sample population age norms for visual acuities obtained with Vistech-Teller Acuity Cards. *Invest Ophthalmol Vis Sci* 1995; 36:657-70.
15. Kriss A. Skin ERGs: their effectiveness in paediatric visual assessment, confounding factors, and comparison with ERGs recorded using various types of corneal electrode. *Internat J Psychophysiol* 1994;16:137-146.
16. Hennessy MP, Vaegan. Amplitude scaling relationships of Burian-Allen, gold foil and Dawson, Trick and Litzkow electrodes. *Doc Ophthalmol* 1995; 89:235-248.
17. McCullough DL, Van Boemel GB, Borchert MS. Comparison of contact lens, foil, fiber and skin electrodes for patterns electroretinograms. *Doc Ophthalmol* 1998;94:327-340.

18. Dutton GN, Jacobson LK. Cerebral visual impairment in children. *Semin Neonatol* 2001;6:477-485.
19. Jacobson KJ, Dutton GN. Periventricular leukomalacia: an important cause of visual and ocular motility dysfunction in children. *Surv Ophthalmol* 2000;45:1-10.
20. Breceelj J, Stirn-Kranjc B. Visual electrophysiological screening in diagnosing infants with congenital nystagmus. *J Clin Neurophysiol* 2004;115:461-470.
21. Lorenz B, Gampe E. Analysis of 180 patients with sensory defect nystagmus (SDN) and congenital idiopathic nystagmus (CIN). *Klin Monatsbl Augenheilkd* 2001; 218:3-12.
22. Flitcroft DI, Adams GG, Robson AG, Holder GE. Retinal dysfunction and refractive errors: an electrophysiological study of children. *Br J Ophthalmol* 2005;89:484-488.
23. Marr JE, Halliwell-Ewen J, Fisher B, Soler L, Ainsworth JR. Associations of high myopia in childhood. *Eye* 2001;15:70-74.
24. Kelly JP, Crognale MA, Weiss AH. ERGs, cone-isolating VEPs and analytical techniques in children with cone dysfunction syndromes. *Doc Ophthalmol* 2003;106:289-304.
25. Alagaratnam J, Sharma TK, Lim CS, Fleck BW. A survey of visual impairment in children attending the Royal Blind School, Edinburgh using the WHO childhood visual impairment database. *Eye* 2002;16:557-561.
26. Blohmé J, Törnqvist K. Visually impairment in Swedish children. III. Diagnoses. *Acta Ophthalmol Scand* 1997;75:681-687.
27. Hansen RM, Flage T, Rosenberg T, Rudanko SL, Viggosson G, Riise R. Visual impairment in Nordic children. III. Diagnoses. *Acta Ophthalmol (Copenh)* 1992;70:597-604.
28. Rahi JS, Cable N. Severe visual impairment and blindness in children in the UK. *Lancet* 2003; 362:1359-1365.
29. Rosenberg T, Flage T, Hansen E, Riise R, Rudanko SL, Viggosson G, Törnqvist K. Incidence of registered visual impairment in the Nordic child population. *Br J Ophthalmol* 1996;80:49-53.
30. Flanagan NM, Jackson AJ, Hill AE. Visual impairment in childhood: insights from a community-based survey. *Child Care, Health Dev* 2003;29:493-499.
31. Kocur I, Resnikoff S. Visual impairment and blindness in Europe and their prevention. *Br J Ophthalmol* 2002;86:716-722.
32. Loewer-Sieger DH. The prevalence of severe visual impairment in children in the Netherlands. *Child Care Health Dev* 1975;1:275-278.
33. World Health Organization. International statistical classification of diseases and related health problems. Tenth revision. Vol 1. Geneva: WHO, 1992:457.

34. Tremblay F, Parkinson JE. Alteration of electroretinographic recordings when performed under sedation of halogenate anesthesia in a pediatric population. *Doc Ophthalmol* 2003;107:271-279.
35. Weleber RG, Tongue AC. Congenital stationary night blindness presenting as Leber's congenital amaurosis. *Arch Ophthalmol* 1987;105:360-365.
36. Sundin OH, Yang JM, Li Y, Zhu D, Hurd JN, Mitchell TN, Silva ED, Maumenee IH. Genetic basis of total colourblindness among the Pingelapese islanders. *Nat Genet* 2001;25:289-93.
37. Zeitz C / Van Genderen M, Neidhardt J, Luhmann UF, Hoeben F, Forster U, Wycisk K, Matyas G, Hoyng CB, Rienslag F, Meire F, Cremers FP, Berger W. Mutations in GRM6 cause autosomal recessive congenital stationary night blindness with a distinctive scotopic 15-Hz flicker electroretinogram. *IOVS* 2005;46:4328-35.
38. Yzer S, van den Born LI, Schuil J, Kroes HY, van Genderen MM, Boonstra FN, van den Helm B, Brunner HG, Koenekoop RK, Cremers FP. A Tyr368His RPE65 founder mutation is associated with variable expression and progression of early onset retinal dystrophy in 10 families of a genetically isolated population. *J Med Genet* 2003;40:709-13