Principles and Practice of Clinical Electrophysiology of Vision

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A Year Book Medical Publishers imprint of Mosby-Year Book, Inc.

Mosby-Year Book, Inc.
11830 Westline Industrial Drive
St. Louis, MO 63146

1 2 3 4 5 6 7 8 9 0 CL CL MV 95 94 93 92 91

Library of Congress Cataloging-in-Publication Data
Principles and practice of visual electrophysiology / [edited by]
John R. Heckenlively, Geoffrey B. Arden.
p. cm.
Includes bibliographical references.
Includes index.
ISBN 0-8151-4290-0
1. Electroretinography. 2. Electrooculography. 3. Visual evoked response. I. Heckenlively, John R. II. Arden, Geoffrey B. (Geoffrey Bernard)
[DNLM: 1. Electrooculography. 2. Electrophysiology. 3. Electroretinography. 4. Evoked Potentials, Visual. 5. Vision Disorders—physiopathology. WW 270 P957]
RE79.E4P75 1991 91-13378
617.7 1547—dc20 CIP
DNLM/DLC
for Library of Congress

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Multiple Sclerosis

Graham E. Holder

Multiple sclerosis (MS) is a disease of unknown etiology that principally affects the white matter of the central nervous system (CNS) and results in disseminated patches of demyelination. In the first stages of the disease there is usually a relapsing-remitting course; following an acute episode there will be recovery that may appear complete, but as the disease advances, the clinical picture often becomes that of a progressive disease. The initial presentation is usually that of a focal neurological disturbance, and the diversity of symptoms that may occur, e.g., motor weakness, impaired vision, paresthesias, dysarthria, ataxia, bladder dysfunction, etc., can cause diagnostic difficulty in the early stages. This problem is compounded by the lack of a definitive laboratory investigation with which to establish the diagnosis. As the disease progresses and there is evidence of multiple remitting-relapsing lesions disseminated in time and space, the diagnosis usually becomes certain.

An acute plaque contains a clearly defined area of demyelination with macrophages containing the products of myelin breakdown.[89] There is lymphocytic perivascular cuffing; this is in keeping with the theory that destruction of the myelin sheath is in some way mediated by the immune system. Plaques most frequently occur in the optic nerves, the spinal cord, the medulla, and the periventricular white matter.[51] In a chronic plaque there is gliosis with densely interwoven astrocyte processes. Many axons are spared, but there is a variable degree of axonal degeneration.[2] The main pathophysiological effects of demyelination are reduced conduction velocity, conduction block, and an impaired ability to conduct fast trains of stimuli due to an increased refractory period.[59] It was estimated that a 1-cm lesion would cause the conduction time to increase from 1 to 25 ms.

Following a report of flash visual evoked potential (FVEP) amplitude reduction in optic neuritis,[78] latency changes in the FVEP were then described in MS.[63, 73] A major advance came in a series of reports from Halliday and colleagues.[26–30] These demonstrated that there is an extremely high percentage of delayed pattern-reversal VEPs (PVEP) following an attack of optic neuritis and, more important, that the PVEP is frequently abnormal in patients with MS who do not have signs or symptoms of optic nerve disease. It is this electrophysiological demonstration of clinically silent lesions in the CNS that can help establish the diagnosis of MS and that may alter management, particularly of a patient presenting with a spinal cord lesion where the need for myelography may be obviated. There was a correlation between amplitude changes in the PVEP and the degree of visual acuity reduction, but no relationship with PVEP latency. Many reports have subsequently confirmed the high incidence of delayed PVEP in demyelination, a summary of these larger studies[3, 9, 11, 13–16, 19, 21, 22, 25, 36–38, 40, 44–46, 49, 50, 52, 53, 55, 58, 62, 65–68, 70, 74, 81, 83, 85–88, 91, 93] being presented in Table 112–1. Typical findings are shown in Figures 112–1 to 112–3. Abnormalities of the steady-state VEP have also been demonstrated.[5, 61, 72, 90]

A recent study of magnetic resonance imaging (MRI) and PVEP in optic neuritis demonstrated that the PVEP remains the investigation of choice.[60] The PVEP detected dysfunction in 44 of 44 symptomatic nerves and 8 of 30 asymptomatic nerves; the figures for MRI were 37 of 44 and 6 of 30. Four eyes had abnormal PVEP and negative MRI findings. Two other asymptomatic nerves had MRI evidence of optic

TABLE 112–1.
Incidence of Abnormal PVEP in Multiple Sclerosis*

Reference	Definite	Probable	Possible	PHON†
Halliday et al.[30]	33/34	5/5	11/12	24/24
Asselman et al.[3]	26/31	5/6	3/14	34/51
Lowitzsch et al.[49]	60/73	25/42	13/20	—
Mastaglia et al.[53]	19/23	3/9	12/36	—
Celesia and Daly[11]	29/37	2/6	6/10	22/23
Hennerici et al.[36]	13/16	12/18	10/23	100%
Matthews et al.[55]	46/61	14/24	10/28	30/36
Collins et al.[16]	29/37	15/30	7/31	—
Kayed et al.[45]	22/24	11/18	7/18	100%
Nilsson[66]	15/19	8/9	3/10	13/14
Shahroki et al.[81]	49/60	24/46	12/43	54/62
Clifford-Jones et al.[14]	25/31	8/11	6/20	—
Tackmann et al.[83]	26/27	3/7	9/20	23/25
Trojaborg and Petersen[85]	27/28	7/12	2/10	22/23
Chiappa[13]	113/139	59/113	25/97	105/128
Diener and Scheibler[19]	18/22	18/25	9/21	31/31
Mastaglia et al.[52]	44/52	13/33	21/96	—
Wilson and Keyser[91]	90/100	—	—	62/70
Oepen et al.[68]	65/87	18/35	42/113	44/54
Cohen et al.[15]	67/75	16/25		—
Hennerici and Wist[37]	136/168	110/183	50/129	—
Kjaer[46]	57/58	15/18	27/41	—
Lowitzsch and Maurer[50]	73/93	103/139	113/240	—
Mauguiere et al.[58]	53/63	56/87		—
Riemslag et al.[74]	26/41	10/15	4/12	—
Carroll et al.[9]	58/64	20/28	2/5	—
Walsh et al.[88]	47/56	—	—	—
Oishi et al.[70]	42/51	63/76	122/177	—
Fischer et al.[22]	114/132§	111/164§	192/543§	—
Engell et al.[21]	54/64	—	—	21/22
Morocutti et al.[62]	15/16	9/14	—	11/12
Guerit and Argiles[25]	20/22	19/25	12/18	—
Hume and Waxman[40]	14/14	26/29	31/81	—
Novak et al.[67]	14/16	41/47	35/64	22/23
Uhlenbrock et al.[86]	113/136	—	—	—
		Unclassified		
Zeese[93]		24/26		9/10
Hoeppner and Lolas[38]		54/104‡		30/35‡
Van Dalen and Spekreijse[87]		22/29		6/8
Nikoskelainen and Falck[65]		34/50		94%
Julsrud[44]		46/49		—

*The numbers have been calculated when only percentages were given.
†PHON = previous history of optic neuritis.
‡The findings in this paper are not clearly expressed and have been extrapolated from a combination of tabulated data and a figure showing interocular latency asymmetries.
§These figures have been estimated according to data and percentages given in the paper.

nerve lesions; the PVEPs in both of these eyes were at the upper limits of normal. The failure of the PVEP to demonstrate a definite abnormality in these two eyes and the relatively low incidence of abnormal VEP in "possible" MS (see Table 112–1) lead to the question of how the sensitivity of the test may be enhanced. The use of a patterned stimulus has usually been demonstrated to greatly improve the detection of optic nerve conduction abnormalities when compared with a conventional diffuse flash.[17, 20, 27, 32, 33, 90, 91] However, one report has appeared that describes a significant improvement in abnormality detection with the FVEP.[39] We routinely record both PVEP and FVEP in patients sus-

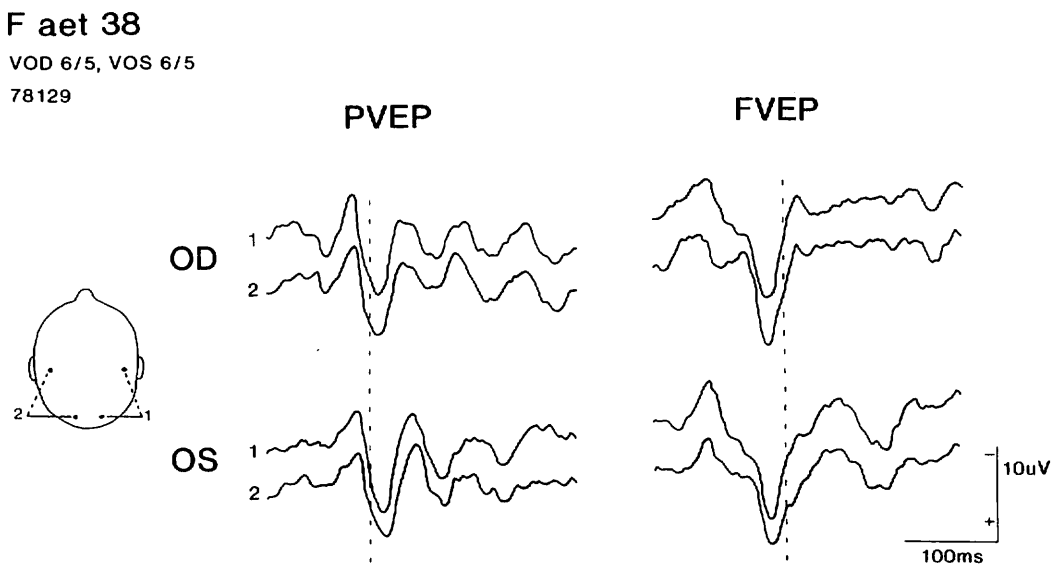

FIG 112–1.
PVEPs and FVEPs in a 48-year-old woman with progressive spastic paraplegia due to MS. There were no signs or symptoms of disease outside the spinal cord, but there was an undocumented history of vertigo in her twenties. Note the bilateral delay in the PVEPs but the normal FVEPs. The *broken vertical lines* represent the upper limits of normal latency (mean + 3 SD).

pected of MS and cannot confirm this finding based on observations in considerably more than 1,500 patients with MS (Holder, unpublished data). Visual acuity can be severely impaired in an acute optic neuritis with associated extinction of the PVEP; the FVEP is particularly useful (Fig 112–4) in such circumstances. FVEPs may also be useful in the rather uncommon situation of a patient with severe nystagmus when fixating on the pattern and an unrecordable PVEP.

There have been many attempts to improve sensitivity by manipulation of pattern stimulus parameters. The use of small (10- to 30-minute) checks has usually been found to increase abnormality detec-

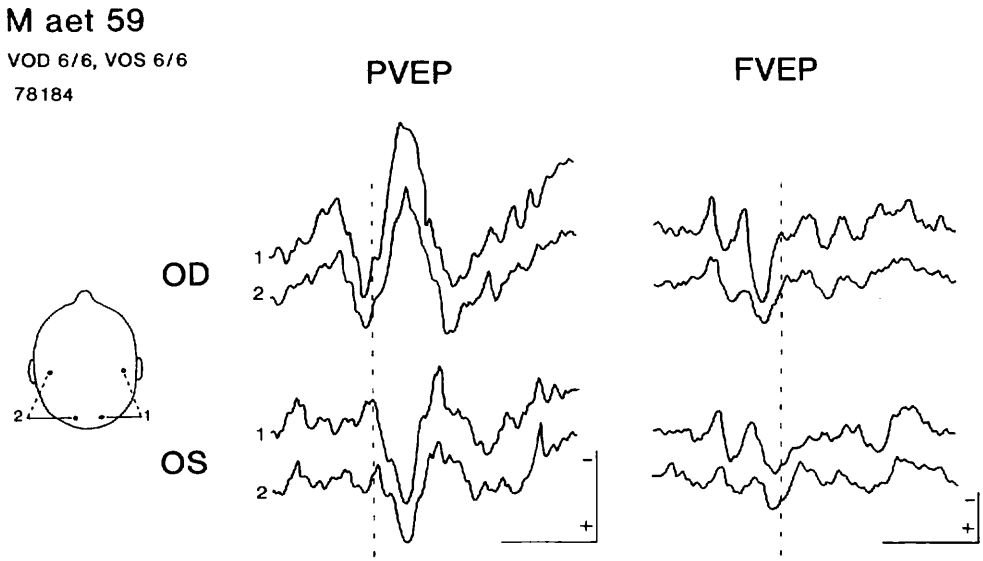

FIG 112–2.
PVEPs and FVEPs in a 59-year-old man with clinically definite MS. There were no signs or symptoms of optic nerve involvement. Note the gross unilateral delay in the PVEPs with only relatively mild changes in the FVEPs. The *broken vertical lines* represent the upper limits of normal latency (mean + 3 SD) (calibration, 100 ms, 10 μV).

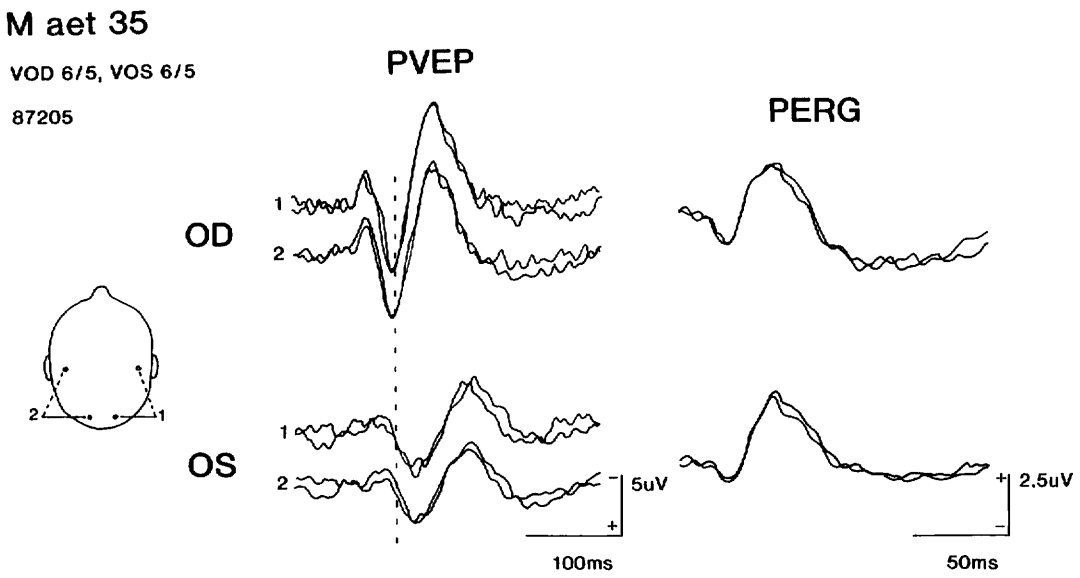

FIG 112–3.
PVEPs and pattern electroretinograms (PERGs) in a 35-year-old man with a progressive spastic paraplegia. The left optic disc was thought to be paler than the right but not to demonstrate frank optic atrophy. The left eye *(OS)* PVEP is markedly delayed; the left eye PERG shows a significant reduction in the N95 component (the intraocular N95:P50 ratio should be $\geq$1.1 and is 1.3 for OD but 0.9 for OS). There is no interocular asymmetry in the P50 component. The right eye PERG is normal, the PVEP P100 component falling just within the normal range. The *broken vertical line* represents the upper limits of normal latency (mean + 3 SD). (From Holder GE: The incidence of abnormal pattern electroretinograms in optic nerve demyelination. *Electroencephalogr Clin Neurophysiol* 1991; 78:18–26. Used by permission.)

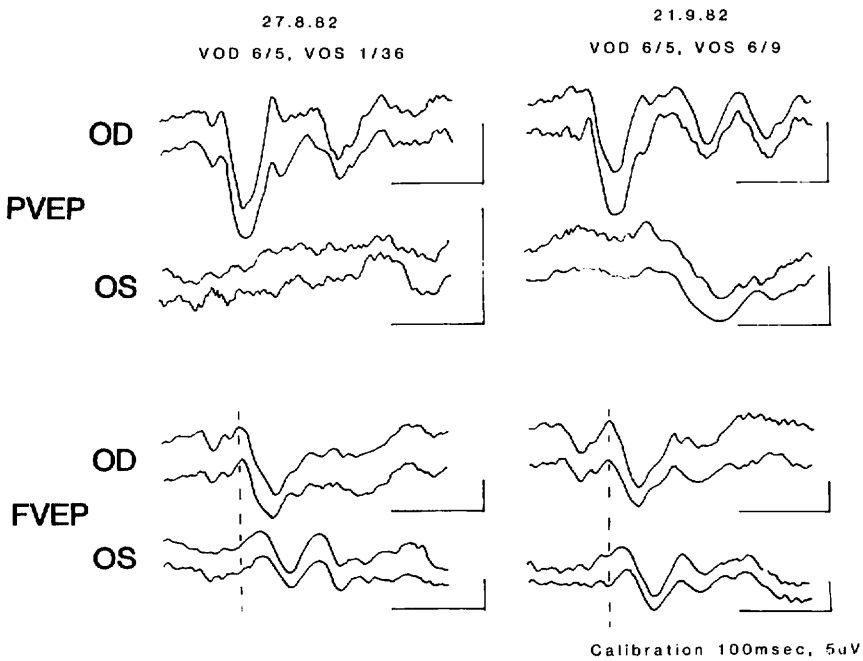

FIG 112–4.
PVEPs and FVEPs in a 23-year-old woman during and 1 month following acute retrobulbar neuritis in the left eye *(OS)*. Right eye findings are normal. The left eye PVEP is initially extinguished but 1 month later has returned with a grossly increased latency. The FVEP is initially severely delayed. Although there is some improvement during the follow-up period, the FVEP remains markedly abnormal. The *upper* and *lower traces* in the recordings from each eye represent the right and left hemispheres, respectively, similar to other figures in this chapter. Positivity is downward. Note the differences in calibration.

tion[24, 25, 58, 61, 64, 67, 70] but not in all studies.[32] A high spatial frequency is best if a grating stimulus is used.[71] However, a comparison of grating and checkerboard stimuli in MS suggests that many patients have orientation-specific abnormalities to gratings and that a checkerboard, possibly due to its greater complexity, maximizes abnormality detection.[7] The use of a small central field stimulus can improve abnormality detection,[6, 31, 35, 70] but is most efficient when additionally combined with half-field stimulation using a large-field/large-check stimulus.[6, 31] Hemifield stimulation will also help in the detection of chiasmal or retrochiasmal dysfunction.[60, 75] Some authors[19, 36, 37, 92] find foveal luminance stimulation to be more effective than a checkerboard or a diffuse flash,[77] but not all reports confirm these findings.[68] Foveal stimulation with a light-emitting diode (LED) array may give increased sensitivity.[17, 57, 66, 76] Mauguiere's group[57] studied 125 patients and reported that 18 patients had abnormalities with the LED stimulus that were not present with a checkerboard. The percentage of absent VEPs is, however, increased. Reductions in stimulus contrast[58] or luminance[8] may be advantageous, but other authors fail to agree that luminance reduction has any definite benefits.[37] The use of pattern-onset/offset stimulation is advocated by some authors to be more effective than reversal,[74] but this is also disputed.[33, 84] One recent report used both pattern reversal in conjunction with different check sizes and variations in luminance and pattern-onset stimulation with variations in check size and contrast in a study of patients with optic neuritis.[79] The VEP amplitude, independent of stimulus configuration, was related to clinical tests of visual function (Snellen acuity, color vision, visual fields, contrast sensitivity), with no such relationship observed for VEP latency. The VEPs in unaffected eyes were most likely to be abnormal with 60-minute-check, pattern-reversal stimulation at the highest luminance used.

The need for accurate interpretation of a delayed VEP cannot be overstressed. The initial task of the visual electrophysiologist is to ensure that the "delay" is genuine and is not a result of component misidentification; waveform changes are frequently seen. When a large-check/large-field stimulus is used (and only such a stimulus), the paramacular P135 component, seen with, e.g., a 5- to 16-degree annular hemifield in normals, may predominate if there is a central scotoma and may be mistaken for a delayed P100 component.[4, 47] This is particularly true if a single midline recording channel is used that precludes assessment of individual hemisphere responses; such a combination cannot be recommended under any circumstances. The use of a small central field will give the macular P100 component, and the "delay" can be correctly assessed. Perhaps the most efficient analysis may be provided by a combination of (1) a small-field, small-check, full-field stimulus and (2) a large-check, large-field, hemifield stimulus. It is also essential that the delayed PVEP that can occur as a result of macular or other distal anterior visual pathway dysfunction not be misinterpreted as optic nerve disease. PERG recording will usually enable this distinction, and the reader is referred to Chapter 70 for a full discussion of the use of the PERG in optic nerve dysfunction, including an illustration of PERG findings in a developing optic neuritis. Although most pertinent to the patient with visual symptoms, the PERG can also be useful in excluding or establishing refractive error or amblyopia, both common incidental findings, as a cause of delayed PVEP in the patient with a single spinal cord lesion in whom myelography is being considered and in whom other modality evoked potentials have failed to indicate a lesion apart from what is clinically demonstrable.

It is also important, having determined that a PVEP delay is not due to distal anterior visual pathway dysfunction, that such a delay not be automatically assumed to reflect optic nerve demyelination due to MS. Delays can occur in optic nerve or chiasmal compression (see Chapter 71), toxic amblyopia,[47] sarcoidosis,[82] ischemic optic neuropathy (see Chapter 83), Friedreich's ataxia,[10] vitamin B_{12} deficiency,[48] and other conditions,[12] sometimes with and sometimes without symptoms of optic nerve disease. The PVEP findings can only be accurately interpreted in clinical context; the taking of an accurate history and competent neurological and ophthalmological examination should be a prerequisite in all patients. Examination of the cerebrospinal fluid (CSF) may show a few lymphocytes, an increased proportion of IgG in total CSF protein, or oligoclonal bands on electrophoresis, but the findings are not specific for MS, and the delay in obtaining the latter result often precludes its use in the immediate management of the patient. Other modality evoked potentials may reveal clinically silent lesions. Neuroradiological examination with high-resolution CT scanning or MRI may show multiple lesions, and indeed recent reports indicate that MRI will often demonstrate additional lesions in acute optic neuritis and no signs or symptoms of disease outside the optic nerve[43, 60, 69, 80]; currently, however, MRI is expensive and not always readily available. A re-

cent follow-up study (mean, 11.6 years) of 146 patients in the United Kingdom who presented with isolated idiopathic optic neuritis reported that 57% had developed MS by the time of reassessment, 51% with clinically definite disease.[23] There is an increased risk of MS in patients with HLA-DR2 tissue types.[23, 34] An actuarial analysis of a different series calculated that more than 75% of patients will have developed MS by 15 years following optic neuritis.[41] Obviously these figures may not apply to other countries given the known racial and geographical factors involved in the development of MS.[1]

There have so far been relatively few reports of serial or follow-up studies that may further define the value of the VEP (or other modality evoked potentials). One study of clinically definite MS patients reported an increased incidence of abnormal multimodality evoked potentials with a 2-year follow-up period.[88] Although there was generally deterioration, PVEP latency reduction was observed in 9 of 112 eyes. Another follow-up study of definite MS patients[42] found that clinical relapse was accompanied by evoked potential deterioration and that the evoked potential changes could occur during remission periods in the absence of clinical changes. Hume and Waxman[40] used a 2½ year follow-up and found that 78% of patients with PVEP demonstration of a clinically silent lesion in MS suspects showed clinical deterioration. Eight patients (5.9%) who progressed to "definite" MS had normal PVEPs. Deltenre and colleagues[18] reported a prospective study of 273 patients with up to a 5-year follow-up. Fifty-six patients evolved to definite MS; 37 of these had had abnormal PVEPs. All the previous follow-up studies used multimodality evoked potentials. Hely et al.[35] reported normalization of PVEP following isolated optic neuritis. Normal PVEPs at follow-up were observed in 9 of 98 eyes, only 1 of these being in a patient who had developed MS. Matthews and Small[54] described PVEP normalization in 9 eyes of 51 patients recorded at varying intervals, the same group reporting a case where a grossly abnormal PVEP after 3 years' serial follow-up returned to normal after a further 3½ years; the other eye had meanwhile become grossly abnormal.[56]

In conclusion, there are two groups of patients who will present to the visual electrophysiologist: one has acute visual loss due to suspected optic neuritis, and the other has disease elsewhere in the CNS that is suspected to be MS and is referred for possible VEP detection of optic nerve demyelination. It is likely that some of these patients may previously have suffered an attack of optic neuritis. The need for accurate component identification and the exclusion of causes outside the optic nerve for a delayed PVEP are again noted. It is also essential that an accurate history be taken and a comprehensive ophthalmic and neurological examination performed. The VEP findings can then be meaningfully evaluated in the clinical context.

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