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

91

Best's Disease

Hansjoerg E. Kolder

Best's disease is an autosomal dominant, pleomorphic, progressive, retinal pigment epithelium disease beginning early in life. Initially good vision is maintained, but a reduction of the light response of the electro-oculogram (EOG) in a patient with a characteristic macular lesion and an autosomal dominant family history is diagnostic (Fig 91–1,A–C, Plate 19).[16, 20, 29, 33, 79, 90]

Although originally most likely observed more than 100 years ago by Adams,[1] Falls in 1966 is credited with popularizing the term *Best's disease*.[24] Best reported in 1905[11] "Über eine hereditäre Makulaaffektion." He described bright reddish, round, well-delineated, bilateral lesions that resembled central chorioretinic scars in two generations of one family living near the university town Giessen in Germany. Vision was good and remained so for a long time. The youngest patient was 9 years old. The family originally examined by Best was subsequently further evaluated and included by the midtwenties about 300 members, 22 of them affected.[21] Best did not report the "classic" ophthalmoscopic finding of an "egg yolk" lesion.

CLINICAL OBSERVATIONS

The spectrum of evolving clinical manifestations of Best's disease led to descriptive terms[48] like vitelliform,[44] pseudovitelliform,[26] and vitelliruptive.[10, 34, 49, 50] The visible subretinal lesion is small, one-half to three disc diameters, slightly elevated, yellow or orange, foveal or eccentric, single or multiple.[57] The retinal periphery and the optic nerve are not involved ophthalmoscopically. Affected family members may have no fundus changes initially.[8, 60] Hyperopia, astigmatism, strabismus, and amblyopia have been associated with Best's disease. The overlying retina is undisturbed and the vasculature normal. The fluorescein angiogram is initially normal; later blockage is observed.[17, 56, 62] The stages of Best's disease are listed in Table 91–1.

No treatment is available for patients with Best's disease. The electrophysiological distinction between vitelliform dystrophy and pattern dystrophy has practical importance for clinical and genetic counseling. Systemic steroids have been advocated for patients who experience retinal edema and/or hemorrhage while their disease progresses through the resorption stage. Focal laser treatment may be offered when neovascularization appears.[58, 66]

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes many macular afflictions. A considerable overlap exists in terminology, and one treads on thin ice when trying to accommodate as many terms as suggested. Pattern dystrophy has a particular similarity to the late manifestations of Best's disease ("scrambled eggs").[15, 32, 40, 54, 72, 85] The differential diagnosis is given in Table 91–2.

Numerous authors have attempted a rational classification of macular diseases.[28] Deutman,[21] Krill (posthumously published in 1977),[49] and Zinn and Marmor[90] more recently described in detail the history, clinical pathology, and variability of manifestations of Best's disease. Many historical pearls and references are quoted by Deutman, who also extensively reviewed the literature not published in English. Deutman as well as Krill documented in detail

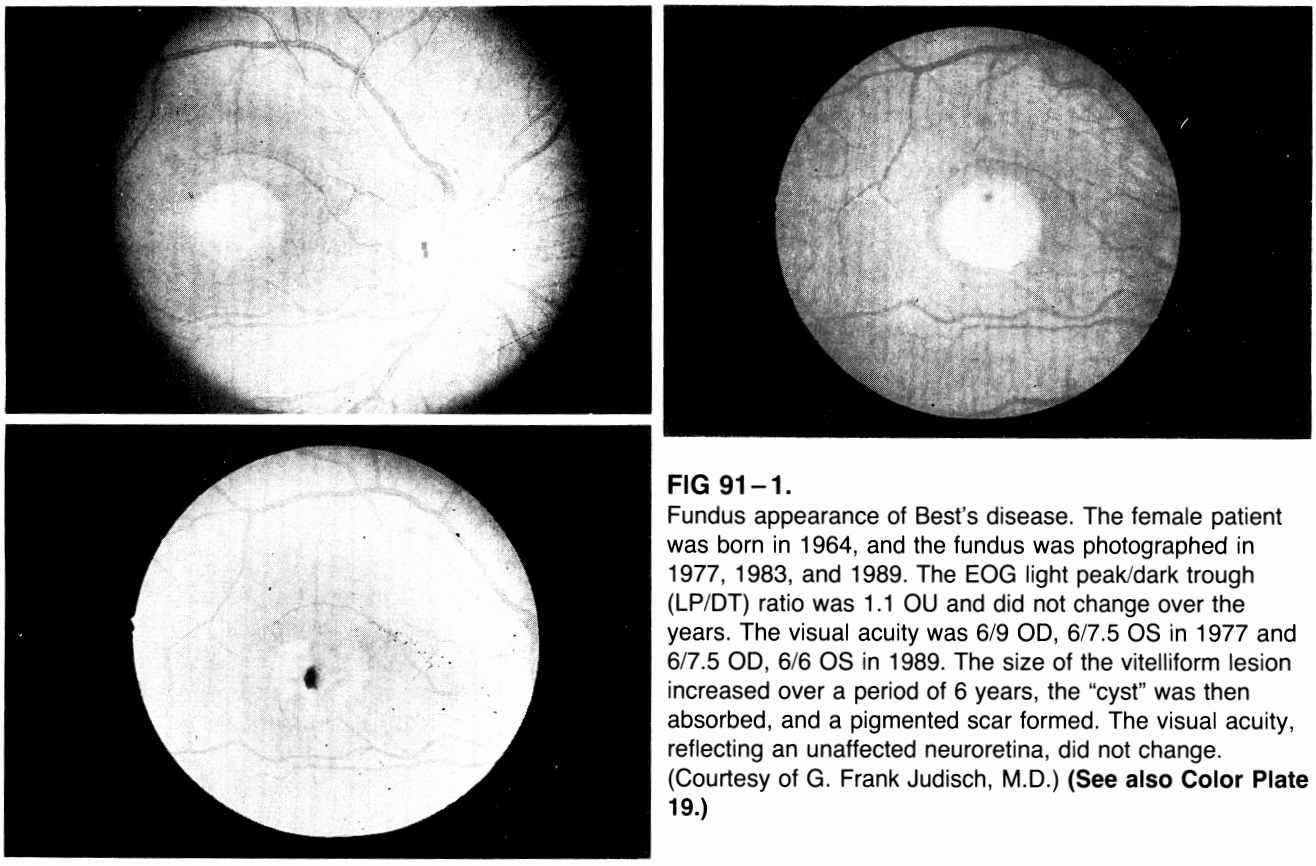

FIG 91–1.
Fundus appearance of Best's disease. The female patient was born in 1964, and the fundus was photographed in 1977, 1983, and 1989. The EOG light peak/dark trough (LP/DT) ratio was 1.1 OU and did not change over the years. The visual acuity was 6/9 OD, 6/7.5 OS in 1977 and 6/7.5 OD, 6/6 OS in 1989. The size of the vitelliform lesion increased over a period of 6 years, the "cyst" was then absorbed, and a pigmented scar formed. The visual acuity, reflecting an unaffected neuroretina, did not change. (Courtesy of G. Frank Judisch, M.D.) **(See also Color Plate 19.)**

families and the functional abnormalities of vision in affected members. These authors established beyond doubt the inheritance, variability, and etiology of Best's disease.

HISTOPATHOLOGY

An important contribution was made to the pathophysiology of Best's disease by Braley,[13] Weingeist et al.[86] and Stone and associates,[77, 88] who used three different and supplementary techniques on members of one large family cohort living in Iowa. In 1964 Braley and Spivey reported clinical details,[13] Blodi[12] and later Weingeist et al.[86] obtained specimens for histological examination, and Stone and associates[77, 88] studied the genetic linkage permitting the differential diagnosis between Best's disease and pattern dystrophy on a molecular basis. The clinical examination employs the standard tools of an ophthalmologist, including fluorescein angiog-

TABLE 91–1.
Stages of Best's Disease

Previtelliform
EOG response to light reduced in all stages
Normal macula
Window defect in fluorescein angiography
Vitelliform
"Egg yolk," "sunny-side up," blocking of choroidal fluorescence on angiography
Pseudohypopyon
Resorption
Vitelliruptive
"Scrambled eggs"
Atrophy
Macular scar
Neovascularization

TABLE 91–2.
Differential Diagnosis, With Synonyms, of Best's Disease

Pattern dystrophy (AD)*
Pseudovitelliform dystrophy
Pseudo–Best's macular degeneration (AD?)
Butterfly-shaped pigment dystrophy (AD)
Foveomacular vitelliform dystrophy[14]
Pseudoinflammatory macular dystrophy[23]
Recessive inherited pseudoinflammatory dystrophy
North Carolina dystrophy (AD)
Solar retinitis
Fundus flavimaculatus with central involvement[27]

*Autosomal dominant disorder.

TABLE 91–3.
Histopathology of Best's Disease

Bruch's membrane intact, but with calcific degeneration
Retinal pigment epithelium structurally intact, but with widespread lipofuscin accumulation
Lipofuscin (orange-colored) granules (recognizable by autofluorescence) are in
Cytoplasm
Macrophages
Subretinal space
Choroid
Lipofuscin probably originates from phagocytosis of outer segments of receptors, is a metabolic end product that resists further lysosomal degradation, and therefore accumulates extracelluarly and intracellularly

raphy.[62] The recording of an EOG has become routine. Histopathological evaluation utilizes light microscopy, electron microscopy, and special stains as readily available tools.[67] Table 91–3 summarizes the histopathology evaluated in an eye of a patient with Best's disease who had a complete eye examination, including an EOG, 1 year prior to his death following a motor vehicle accident at the age of 27 years. Several other histological examinations of eyes with Best's disease have been reported, but the patient of Weingeist et al. is the youngest and had the most complete clinical documentation antemortem.

LINKAGE ANALYSIS

Linkage analysis[89] is used for mapping an observable trait to an identifiable position in a chromosome and investigates genetic heterogeneity. It is a necessary first step in isolating the gene that causes a disease. The principle is to find a large pedigree and to determine whether the gene causing a disease, e.g., "atypical vitelliform macular dystrophy," is on a different chromosome than the gene ("genetic marker") that encodes a known trait.[25] If the disease and the known trait are inherited together and the location of the genetic marker is known, one can assume that the disease-causing gene is located on the same chromosome.

Linkage of the atypical vitelliform macular dystrophy to the locus of glutamate pyruvate transaminase (GPT-1) on chromosome 8 has been reported. The statistical likelihood is high and has a lod (logarithm of odds) of 4.3. In other words the pedigree with atypical vitelliform macular dystrophy is 22,000 times more likely to be linked to GPT-l than not. The use of genetic markers is a relative recent development and confirms a diagnosis. Once that is accomplished, genetic counseling,[7] identification of carriers,[83] and the investigation of biochemical mechanisms are possible. Patients with classic Best's disease are not linked to the GPT-1 locus.

ELECTROPHYSIOLOGICAL TESTS

Which tests are available for corroborating the diagnosis of Best's disease?

On first sight it seems easy to diagnose Best's disease clinically, at least in its classic, vitelliform stage. The diagnosis of Best's disease can be "proved" by testing the LP/DT (Arden) ratio of the EOG. This is true in principle, but several similar clinical manifestations with different prognoses require attention. Also, the EOG is a "crude" test in its present application.[2, 61, 91]

The electroretinogram (ERG) a-wave and b-wave, when evaluated for amplitude and implicit time, contributes little to substantiate the diagnosis of Best's disease. Psychophysically measured dark adaptation has been reported to be delayed. The amplitude of the scotopic ERG takes more time to increase in dark.[52]

The ERG c-wave in Best's disease has been recorded.[64, 65, 69, 71] The authors found that the same or more information can be deduced from the c-wave as from the EOG. The c-wave recording requires a cooperative patient and special direct current (DC) coupling. The test per se takes less time than does the recording of an EOG. The reports need to be substantiated.

Measurement of the fast oscillation (FO)[46, 68, 80, 82, 87] of the EOG takes much less time than measurement of the slow oscillation.[19] Since the light intensity varies every 70 to 80 seconds, patients tear easily, thus introducing an artifact into the recording. Also, in order to obtain good resolution for the phenomenon, eye movements should be repeated every 5 seconds, which tends to dry out the cornea and is uncomfortable for some patients. The FO reflects an electrophysiological event that is robust; Best's disease does not affect the FO. No comprehensive model for the evaluation of parameters of the FO has been reported.

The slow oscillation of the EOG is utilized in an abbreviated form to test the "pigment epithelium."[45, 70, 81, 87] By exposing the eye to darkness for 10 to 15 minutes the "dark trough" of the slow oscillation of the EOG is attained. Following stimulation with light the "light peak" of the slow oscillation occurs within 8 to 13 minutes. Conventionally only the lowest potential in dark and the highest potential in

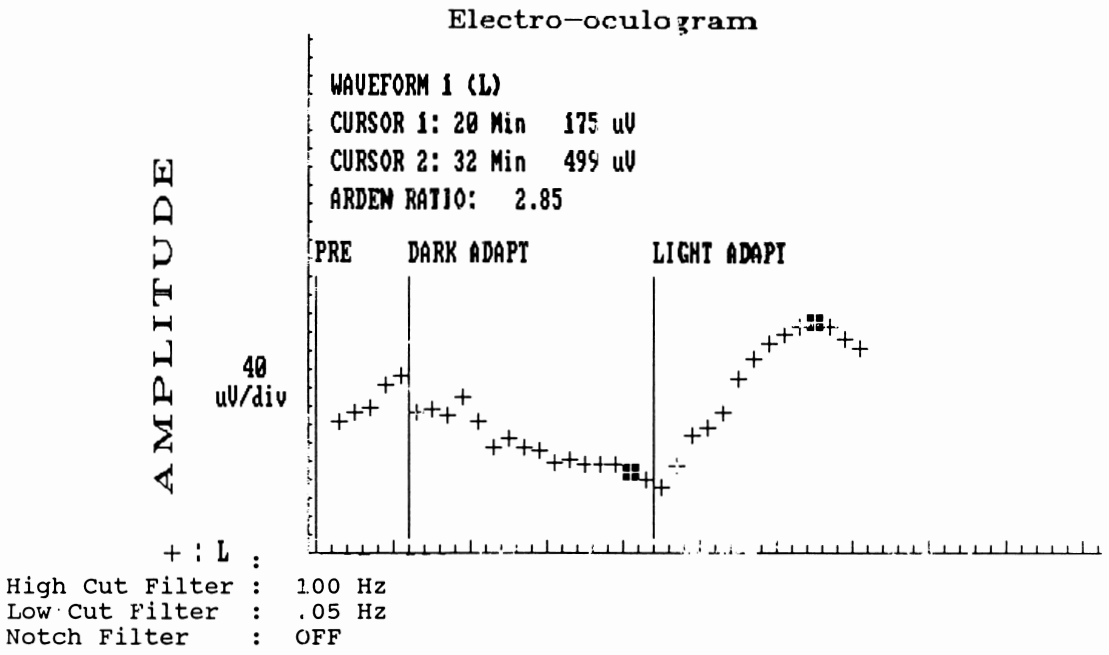

FIG 91–2.
Original tracing of an EOG from a test subject without known eye disease. The EOG was recorded during dark adaptation and subsequent Ganzfeld illumination providing 475 lumen · m^{-2} at the eyes; the abscissa is in minutes, and the ordinate is in microvolts. The EOG potential created by eye movements over an angle of 30 degrees is sampled during 15 seconds of each minute and displayed as an average.

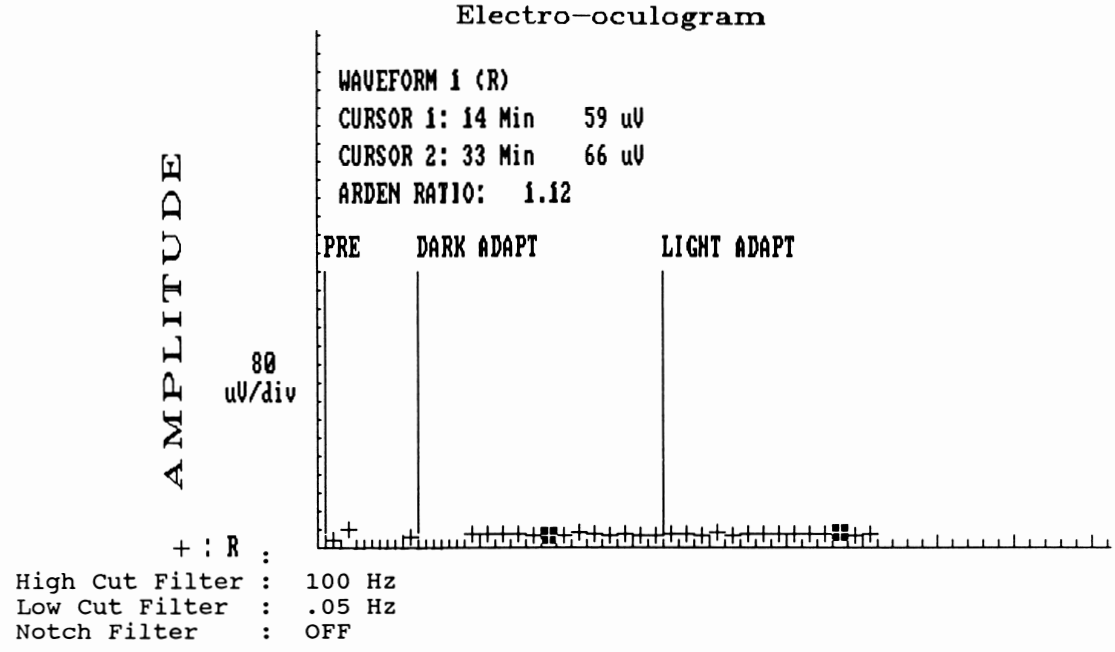

FIG 91–3.
EOG from a patient with Best's disease. The same stimulus and recording conditions were used as mentioned in Figure 91–2. No noticeable light rise was observed during light stimulation.

light are measured and reported as the LP/DT ratio, or Arden ratio. The test is relatively easy to perform, requires encouragement of the patient to continue to make full eye movements, and causes few if any complications. Even children aged 5 to 7 years usually do well when tested by EOG.

The light rise of the slow potential of the EOG is light intensity dependent,[4, 30, 38, 41] sensitive to color,[6] and sensitive to the size of the stimulus[22, 51, 78] (Fig 91–2).

The EOG response is nonlinear when tested with sinusoidally varying light.[9] The details of the dampened oscillatory phenomenon can be simulated[81] by an inductive model assuming information transfer through three or four steps with feedback.[37] The model has seven or nine parameters that can be estimated.[39] Unfortunately, the solution of the set of differential equations consumes considerable computer time. The model has therefore not been tested extensively to refine analysis of the EOG response.

Another approach to expand the scope of usefulness of the EOG employs nonspecific stimuli like acetazolamide,[43, 59] adrenalin,[83] and others.[18, 42, 53, 55, 74, 84] Although promising, not enough information has been gathered on the EOG response to aphotic stimuli in diseased states.

Best's disease affects the pigment epithelium primarily. An analysis of the function of more proximal parts of the visual pathway is unlikely to be heuristic. The ERG oscillatory potentials (OPs), the pattern ERG (PERG), and the visual evoked response (VEP) are unlikely to become diagnostic for Best's disease.

The diagnosis of Best's disease can often be made from clinical observations, examination of family members, and an evaluation of the family tree. The confirmation is dependent on the EOG (Fig 91–3). Even in family members who show no evidence of a pigment anomaly, an abnormal LP/DT ratio identifies patients who can be expected to progress to funduscopic manifestations or who are carriers.

ELECTRO-OCULOGRAPHIC TECHNIQUE

Fortuitously, at a time when Best's disease was established as a separate clinical entity, the technique of recording the EOG had progressed to permit reproducible and reliable recordings of first the slow oscillation of the EOG and later also the FO (see Chapter 39). Because the EOG oscillates slowly following a step increase in light intensity and takes an hour or longer to return to baseline with one or more periods, Arden and associates[4, 5] introduced an abbreviated test protocol that forces a light rise after dark adaptation. Arden's protocol can be completed in half an hour. Any clinical EOG measurement requires the cooperation of the patient, who must follow alternatingly activated fixation lights. The patient's visual acuity must be good enough to see the fixation lights (6/60 or better usually), and the patient must not tear excessively or be inattentive and make incomplete eye movements. The difference in potential between two eye positions, often separated by an angle of 30 degrees, is picked up by means of chlorided silver electrodes placed next to the lateral and medial canthus, respectively. The potential thus recorded is about 1 mV. Skin impedance and polarization currents make a direct recording of the EOG unreliable or difficult but possible.[73] The polarization current is thought to be steady for the brief period (500 ms) necessary to complete an eye movement with sufficient time to measure the potential difference created by the eye as it moves. The eye behaves like an electrical dipole inducing an electrical field in periocular tissue. The field strength varies depending on the position of the "dipole." Amplification through a dc system is feasible, although a long–time constant (10 seconds) ac amplifier is acceptable. The Arden ratio (LP/DT), sometimes multiplied by 100, provides a relative measure of the potential that exist between the cornea and the posterior pole of the eye. Depending on light conditions a value of 1.8 is considered normal with an SD of 0.3, but each laboratory performing EOG has to establish its own standards. A multifactorial analysis of the EOG has been published.[47] Electronic signal processing and computer technology[75] permit artifact rejection, signal shaping, summing of potentials, and electronic storage. All these advances have made clinical EOG recording easier, more reliable, and reproducible. Care must be taken to avoid a loss of information through filtering or restrictive timing of events, e.g., the FO of the EOG cannot be recorded if sets of eye movements are made only once a minute.

ELECTRO-OCULOGRAM ORIGIN

Steinberg and collaborators[31, 76] investigated the origin of the slow and fast oscillations[35] of the EOG. These authors developed an animal model permitting the direct recording of slow potential changes across the isolated retinal pigment epithelium. In a series of experiments and deductions Steinberg et al. established the generator for the slow and fast oscillations of the EOG within and across the pigment epithelium cell. These authors also correlated the

EOG potential with the slow component (c-wave) of the ERG. The electrophysiological origin of the EOG within the pigment epithelium[36, 63] fits in with the histological observation of lipofuscin deposits throughout the retinal pigment epithelium of patients with Best's disease.

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