The Potential for Electrodiagnosis in Glaucoma Diagnosis and Management

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I. Visual evoked potential (VEP)
   A. Definition
      a. An objective measure of visual function that assesses the electrical activity of the cerebral cortex while the subject views standardized visual stimuli
   B. Types of VEP
      a. Flash VEP
         i. Visual stimulus are brief flashes of light
         ii. Resulting waveform is more highly variable between subjects
         iii. Suitable for patients with very poor vision
      b. Pattern VEP
         i. Visual stimulus is a checkerboard, grating, or other patterned stimulus that alternates at a given frequency
         ii. Tends to produce a more robust VEP than flash stimuli
         iii. Size of the pattern can be increased for patients with reduced acuity
      c. Multifocal VEP
         i. Uses a 60-sector checkerboard and electrical responses to pattern stimuli are recorded from 4 electrodes placed over the visual cortex
         ii. Holds potential to act as a form of objective perimetry
         iii. Currently used only in research environments
      d. Short-duration transient VEP
         i. A modified pattern VEP with decreased test duration due to more efficient signal acquisition technique and automated statistical analysis of the waveform enables objective assessment of the VEP waveform
         ii. Clinically available in the Diopsys NOVA system
   C. Equipment
      a. Diopsys NOVA-LX©
         i. Clinically accessible technology that allows for fast and repeatable VEP measurement in office
         ii. Fixed protocol for easier test administration, normative comparison, and progression detection
         iii. Cost, reimbursement, and billable ICD-9 codes
            1. Based on medical necessity
            2. CPT code: 95930
            3. ICD 9 codes: 749.13 (abnormal VEP), 368 (visual disturbance, amblyopias), 300.11 (conversion disorder), 362 (retinal disorder), 377 (optic nerve pathway disorder), 340 (MS), 430-435 (intracran/cerebral), 850-853 (TBI), 907 (late effects), 950 (injury to optic nerve or pathway), V58.69 (long term drug use), 269 (nutritional defic.), 357 (inflam/toxic neuropathy), 909 (late effect poisoning/drug)
            4. 2015 National Medicare Physician (Non-facility) Fee Schedule $129.43
      b. Diopsys NOVA TR©
         i. User-defined protocol
         ii. No comparison of patient results to normative database
D. Set-up
   a. Test conditions
      i. Quiet, darkened room
      ii. Minimal distractions
   b. Electrode placement
      i. Active: Back of scalp (over visual cortex)
      ii. Reference: Forehead
      iii. Ground: Left temple
   c. Scalp and electrode preparation
      i. Scrub site with NuPrep®
      ii. Apply conductive paste to electrode and attach to site with adhesive
      iii. Impedance measurement: The Diopsys NOVA will register whether the electrode impedance is good (green), marginal (yellow), or poor (red)
   d. Testing distance: 1 meter from visual stimulus
   e. Monocular testing
   f. Patient instructions
      i. Importance of attention and concentration

E. Testing
   a. Stimulus presentation
      i. Reversing 32 x 32 checkerboard pattern presented at both high (85%) and low (15%) contrast levels that alternate at 1 Hz (2 reversals/sec)
      ii. Three phases
         1. Warm-up (8 sec): Used to acclimate patient to the test stimulus. No data is collected
         2. Low contrast stimulus presentation (15 sec)
         3. High contrast stimulus presentation (15 sec)
      iii. Music
         1. The Diopsys NOVA LX will by default play soothing music during the stimulus presentation, but the operator has the option of turning this feature off

F. Interpretation
   a. Normal VEP
      i. Waveform
         1. N75- negative trough that occurs around 75ms
         2. P100- positive peak that occurs around 100ms, amplitude is measured from the trough of the N75 to the peak of the P100
         3. N135- negative trough that occurs around 135ms
      ii. Amplitude
         1. Magnitude of the P100 in microvolts from the bottom of the N75 trough to the top of the P100 peak
         2. Vision impairment and disease states may lead to a decrease in the VEP amplitude
      iii. Latency
         1. The amount of time that elapses from the moment the visual stimulus is presented until the peak of the P100 occurs
         2. Disease conditions can result in increased VEP latency
         3. Latency measurements tend to have less variation than amplitude both within-subject and between subjects
b. Printout interpretation
   i. Reliability Index
      1. The P100 Reliability Index indicates the reliability of the P100 amplitude and latency analysis
      2. The reliability index is expressed as a percentage, and may range from 0% to 100%
      3. The index may be interpreted as follows: ≥90% is excellent, 80%-90% is good, 70%-80% is fair, and <70% is poor
      4. In general, a Reliability Index <80% indicates the analysis should be interpreted with caution
   ii. P100 amplitude and latency bar charts
      1. Graphical display of P100 amplitude and latency for each eye
      2. Bars are color-coded to reflect whether they are normal (green), suspect (yellow), or abnormal (red) relative to the instrument’s normative database
   iii. Data Table
      1. Amplitude and latency with color-codes in tabular format
      2. Instrument reports a comment for abnormal results (eg. OD Delayed, Significant Difference, etc)

G. VEP in glaucoma
   a. Early detection
      i. Pillai et al. 2013
         1. Evaluated the ability of the short duration transient VEP (SD-tVEP) to discriminate between healthy eyes and eyes with early to advanced glaucomatous visual field loss
         2. Overall sensitivity of 91.1% and specificity of 93.3%
         3. Low contrast latency demonstrated the highest accuracy for discrimination
      ii. Derr et al. 2013
         1. Evaluated SD-tVEP parameters on patients with pre-perimetric glaucoma
         2. Significant difference in low contrast latency between eyes with pre-perimetric glaucoma and normals
   b. Objective measure of severity and progression
         1. Compared visual field MD and SD-tVEP amplitude and latency in 25 patients with asymmetric glaucoma.
         2. SD-tVEP results correlate significantly with the level of VF damage as measured by MD
      ii. Sponsel et al. 2014
         1. Evaluated the rates of abnormal SD-tVEP amplitude and latency findings in adults with chronic glaucoma
         2. High contrast latency was more sensitive than low contrast latency and amplitude for glaucoma detection and diagnosis of severity based on visual field mean deviation
         3. SD-tVEP amplitude abnormality is rare even in patients with severe glaucomatous visual field loss
II. Pattern Electroretinogram (pERG)

A. Definition
   a. The steady-state pattern ERG is a non-invasive, direct, objective measure of retinal ganglion cell (RGC) function
   b. Measures the mass electrical response of RGCs of the central retina to contrast reversing visual stimuli

B. Types of ERG
   a. Flash
      i. No contribution of RGCs to the conventional flash ERG response
      ii. Photopic negative response can be induced using a red flash on a blue background
   b. Pattern
      i. Response to a high contrast reversing stimulus (checkerboard or stripes)
      ii. Types
         1. Transient pERG
            a. Produced with a slow stimulus reversal rate
            b. Waveform contains N35, P50, N95 components
         2. Steady state pERG (SS-pERG)
            a. Produced with a fast stimulus reversal rate
            b. Generates a sinusoidal-like waveform whose period corresponds to the reversal frequency
            c. Prolonged stimulus exposure leads to an increase in optic nerve blood flow and autoregulatory changes of the neural-vascular system reflecting greater metabolic demand
               i. Sustained stimulus presentation leads to a reduction in amplitude over time even in normal eyes
               ii. These autoregulatory mechanisms may be altered in glaucoma leading to early or excessive fatigue

C. Equipment
   a. Diopsys NOVA©
      i. Clinically accessible technology that allows for fast and repeatable pERG measurement in office
      ii. Automated protocol for easier test administration and progression detection
      iii. Cost, reimbursement, and billable ICD-9 codes
         1. CPT code 92275
         2. ICD 9 codes: 749.11 (abnormal ERG), 368 (visual disturbance), 300.11 (conversion disorder), 362 (retinal disorder), 365.1 (glaucoma), 377 (optic nerve pathway disorder), 249 (secondary DM), 250 (DM), V58.69 (long term drug use), 269 (nutritional defic.), 357 (inflam/toxic neuropathy), 909 (late effect poisoning/drug)
         3. 2015 National Medicare Physician (Non-facility) Fee Schedule $147.67

D. Set-up
   a. Dark room illumination
   b. Limit distractions
   c. Correction- trial frame distance refraction with a +1.50D ADD
   d. 24” testing distance
   e. Prep lower lids with lid scrubs, clean forehead with NuPrep© gel
   f. Electrode placement
i. Lower lid OD - red
ii. Lower lid OS - black
iii. EEG electrode center of forehead - green
g. Monocular testing
h. Patient instructions

E. Testing
   a. Contrast Sensitivity fixed protocol
   b. Stimulus is a reversing 64 bar pattern (15Hz) presented for 25 seconds at both high contrast (Hc, 85%) and low contrast (Lc, 15%) levels

F. Interpretation
   a. Printout
      i. Demographics
      ii. Signal quality indicator
         1. Measures quality of electrode connection
         2. Green is best
      iii. Monocular pERG waveform graphs for Hc and Lc
      iv. Strip Chart
         1. Minimized overview display of the pERG recording throughout the entire test
         2. Peaks indicate artifacts
      v. Frequency distribution plot
         1. Displays the magnitude of the response at differing frequencies
         2. Peak should be present at 15Hz
      vi. Data table
         1. Monocular Magnitude (μV) for Hc and Lc levels
            a. Raw strength of the pERG signal
            b. Larger magnitudes = normal eyes
            c. Color coded normative database comparison for Hc
               i. Green - value is within 96% of the reference population
               ii. Yellow - value is within 2% of the reference population
               iii. Red - value is within the lower 2% of the reference population
         2. Monocular Magnitude D for Hc and Lc levels
            a. Takes into account magnitude and phase variability throughout the test
            b. Color coded normative database comparison for Hc
         3. Monocular Magnitude D/Magnitude ratios (0-1.00) for Hc and Lc levels
            a. Closer to 1.00 (similar Magnitude and Magnitude D values) when the responses are repeatable in magnitude and phase
            b. Color coded normative database comparison for Hc
            c. The most repeatable test-to-test measurement
         4. Signal to Noise Ratio (SNR, dB)
            a. Calculation comparing the strength of the signal at 15Hz (stimulus) compared to the noise
         5. Artifacts
            a. Artifact count including blinks, movement, etc.

G. Normal pERG
   a. Three equally spaced sinusoidal-like peaks
b. Magnitude values greater than 1.2 uV  
c. Similar Magnitude and Magnitude D values  
d. Interfering factors  
   i. Blur  
   ii. Media opacity  
   iii. Macular disease  

H. pERG utility in glaucoma  
a. Overview  
   i. A dynamic test capable of measuring increases or decreases in RGC function over a relatively short period of time  
   ii. Measure of ganglion cell dysfunction, not just RGC death  
   iii. Changes observed in glaucomatous eyes  
      1. Decreased amplitude  
      2. Increased phase variability  
   iv. Association with Humphrey visual field (HVF) testing  
      1. Dissociated in early disease  
         a. Measuring two different parameters  
            i. pERG objectively measures a mass electrical response from RGCs following presentation of a suprathreshold stimulus  
            ii. HVF subjectively measures response to focal threshold stimuli and is influenced by post-retinal factors  
            iii. pERG may be abnormal when the HVF is normal and vice versa  
   b. pERG is often reduced in areas of normal visual field in glaucomatous eyes reflecting generalized RGC dysfunction  
   v. Association with OCT parameters  
      i. pERG amplitude is weakly correlated with RNFL thickness in early glaucoma  
      ii. pERG abnormalities exceed the proportion expected for lost RGC axons in eyes with early glaucoma  

b. Clinical applications  
   i. Earlier detection of glaucoma and prediction of future visual field loss  
      1. Can detect RGC dysfunction in glaucoma suspects with normal baseline perimetry  
      2. Can predict the development of HVF defects in glaucoma suspects with normal baseline perimetry  
      3. Earlier intervention may prevent irreversible death of dysfunctional RGCs  
      4. Bode et al. 2011  
         a. Evaluated pERG in ocular hypertensive eyes followed for a mean of 10.3 years  
         b. Eyes that converted to glaucoma had significantly lower pERG amplitudes  
         c. The pERG amplitude detected glaucoma 4 years before visual field changes occurred, with a sensitivity of 67% and specificity of 64%  
   5. Banitt et al. 2013
a. Evaluated the time lag between loss of RGC function as measured via pERG and RNFL thickness in glaucoma suspect eyes
b. It took 1.9-2.5 years to lose 10% of the initial pERG amplitude, whereas it took 9.9 - 10.4 years to lose 10% of the initial NFL thickness
c. The time lag between pERG amplitude and RNFL thickness to lose 10% of their initial values is on the order of 8 years

ii. Differentiate glaucomatous eyes from normal eyes
1. Urgiles et al. 2014
   a. Evaluated the ability of pERG to discriminate between healthy, glaucoma suspect, and glaucomatous eyes
   b. pERG discriminated glaucoma suspect eyes from normal eyes with 54% sensitivity and 80% specificity
   c. pERG discriminated mild glaucomatous eyes from normal eyes with 87% sensitivity and 93% specificity
2. Mavilio et al. 2015
   a. Evaluated variability of 5 consecutive SS-pERG tests in normal, glaucoma suspect and early glaucoma eyes
   b. pERG amplitude was reduced and CVphase (coefficient of variation of phase) was significantly increased in early glaucoma and suspect eyes compared to normal eyes

iii. Evaluate treatment efficacy
1. pERG can detect reversal of RGC dysfunction in early glaucoma
2. Ventura et al. 2012
   a. Compared the slope of pERG amplitude decline in glaucoma suspect eyes receiving IOP lowering treatment and untreated glaucoma suspect eyes
   b. The rate of pERG amplitude decline slowed in treated eyes compared to the untreated eyes
3. Ventura et al. 2005
   a. Compared changes in pERG following initiation of IOP lowering treatment in eyes with ocular hypertension or glaucoma
   b. In 56% of right eyes and 21% of left eyes of the treated glaucoma subgroup, the pERG amplitude and/or phase improved beyond the 95% confidence intervals of the test-retest variability of the untreated glaucoma control group
   c. pERG improvement with IOP lowering occurred in both high- and low-tension glaucoma eyes
   d. Eyes with severely impaired visual fields showed little improvement in pERG
4. Sehi et al. 2010
   a. Evaluated pre and post-op pERG parameters in glaucomatous eyes undergoing trabeculectomy
   b. Mean postoperative pERG amplitude was significantly increased compared with preoperative pERG amplitude

iv. Objectively monitor progression over time
1. Particularly useful to measure progression in glaucoma suspect eyes with normal visual fields and structural testing
   v. Complement HVF in poor test takers
   vi. Differentiate between ocular and neurologic dysfunction when combined with VEP

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