Cerebral Evoked Potentials in Multiple Sclerosis

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ABSTRACT: Multimodal evoked potentials were analyzed from 58 possible, 62 probable and 100 definite (total 220) multiple sclerosis (MS) patients. Visual evoked potentials (VEP) were most frequently abnormal yielding 39%, 69%, 84% in the three diagnostic groups respectively. Median nerve sensory evoked potentials (SEP) yielded abnormalities in 26%, 65%, 79% respectively. Brainstem auditory evoked responses (BAER) were abnormal in 17%, 39%, 66% respectively. We measured the combined amplitude (CA) of waves III, IV, V in the BAER of these patients as an objective measure of amplitude asymmetry. The CA was considered abnormal if it was 1SD below the lowest CA value in the control group. The CA was abnormal in 9.2% of BAER with normal central conduction time. The BAER diagnostic yield in MS patients increased 11% by using CA analysis.

RÉSUMÉ: Les potentiels évoqués cérébraux dans la sclérose en plaques. Nous avons analysé les potentiels évoqués multimodes chez 58 patents chez qui le diagnostic de sclérose en plaques était possible, 62 patients chez qui ce diagnostic était probable et 100 patients chez qui ce diagnostic était certain. Les potentiels évoquées visuels (PEV) étaient plus fréquemment anormaux, soit 39%, 69%, 84% des cas, dans les trois groupes respectifs. Les potentiels évoqués sensitifs (PES) au niveau du nerf médian étaient anormaux dans 26%, 65%, et 79% des cas respectivement. Les réponses auditives évoquées au niveau du tronc cérébral étaient normales chez 17%, 39% et 66% des cas respectivement. Nous avons mesuré l'amplitude combinée (AC) des ondes III, IV et V dans les réponses auditives évoquées de ces patients comme mesure objective de l'asymétrie des amplitudes. L'AC était considérée comme normale si elle était en deçà de 1DS de la valeur de l'AC la plus basse dans le group témoin. L'AC était anormale dans 9.2% des réponses auditives évoquées dont le temps de conduction central était normal. L'utilisation de l'analyse de l'AC chez les patients souffrant de sclérose en plaques a augmenté le rendement diagnostique de la méthode utilisant les réponses auditives évoquées du tronc cérébral.

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The diagnostic value of evoked potentials in multiple sclerosis (MS) has been emphasized in several recent publications.[1-12] The abnormalities in visual (VEP), brainstem auditory (BAER) and somatosensory (SEP) evoked potentials have been characterized and compared in a few studies.[13-20] All studies have shown a diagnostic yield which increases proportionately to the clinical certainty of the diagnosis. BAER produced the lowest diagnostic yield in most reports. Our study evaluates whether amplitude analysis improves this yield.

MS patients commonly exhibit BAER with normal central conduction time (CCT) but inter-ear amplitude asymmetry. Analyzing this asymmetry has proven difficult due to amplitude variability in normal subjects.[12,21,22,23]

Hoping to improve the diagnostic yield of BAER in MS, we studied the combined amplitude (CA) of waves III, IV, V and the results of this analysis are presented. We also present multimodal evoked potential results in our large series of MS patients relative to the diagnostic categories of possible, probable and definite MS.

Method

Evoked potentials from 220 patients referred from the MS Research Clinic between 1980 and 1984 were analysed retrospectively. The patients were classified clinically as possible, probable and definite MS according to the criteria of Rose,[24] based on the most recent examination prior to testing. There was 100 definite, 62 probable and 58 possible MS patients composed of 135 females and 85 males ranging in age from 13 to 77 years (mean 39). Not all patients had complete multimodal evaluation. The CSF was examined in all patients and some had CT Scan. The interval between clinical exam and evoked potential studies ranged from zero to 32 days (mean 9.5). The duration of the disease prior to the clinical examination varied between 1 week and 40 years.

Control values were obtained by examining medical students, nurses, technicians etc. who had no history or signs of neurological diseases. For VEP, 40 subjects (14 males, 26 females) age 19 to 64 (mean 34.4) were examined. For BAER 34 subjects (12

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males, 22 females) aged 19 to 64 (mean 33.7) were examined. For SEP control data was obtained from 24 different subjects (10 males and 14 females) aged 13 to 54 (mean 25).

VEP Technique

The patients were seated in a dimly lit room and instructed to fixate on a small dot centred on a Nicolet 1006 stimulator screen, located 1 metre from the eye while a black and white checkerboard pattern reversal stimulus was presented at a rate of 0.94 Hz. Eyes were examined independently. The checkerboard square subtended an angle of 1.7°, and the whole screen 11.9° vertically and 16.4° horizontally. The background luminence remained constant throughout the test. The VEP was recorded using tin electrodes, secured with collodion, and filled with conduction jelly. Impedance was less than 5 Kohms. Bandpass was 1 Hz to 30 Hz and recording montage Oz-Cz, (International 10-20 System). The electrodes were connected to a Nicolet HGA-100A amplifier. One hundred responses were averaged, using a Nicolet CA-1000 Clinical Averager. The VEP was obtained at least twice in each eye, to ensure replication, displayed on an oscilloscope for latency measurement and then written out with an X-Y plotter. Latency was measured at the response peak. A VEP was deemed absent, if no reproducible response appeared after 3 trials.

SEP Technique

The median nerve at the wrist was stimulated at 3 Hz by a .2 msec square pulse with sufficient intensity to produce a slight thumb twitch. Tin electrodes with impedance below 5 Kohms were placed over ipsilateral ERB's point, 4 cm below the inion, and 2 cm posterior to contralateral C3 and C4 (international 10-20 system) and referenced to Fz. The response from 250 stimuli was averaged from these 3 sites using a Nicolet HGA-200A amplifier and Nicolet CA1000 averager with bandpass 30-1500 Hz. The waves of interest corresponded to wave EP, P/N13, N19 of Chiappa.[12] Latencies were measured from the triggering pulse to the peak of each wave.

BAER Technique

The response was recorded in a quiet room with a Nicolet HGA-200A amplifier and Nicolet CA-1000 averager from tin electrode applied to ipsilateral ear lobe and referenced to the vertex with the patient recumbent. Electrode impedance was less than 5 Kohms. The contralateral ear was masked with 30 dB white noise if there was greater than 10 dB hearing level (HL) discrepancy between the two ears. Monaural rarefaction clicks were delivered by an earphone (50 Omega telex 1470), 65 dB above HL at the rate of 11.1/seconds with a duration of 100 microseconds. At least two 10 msec samplings were obtained using 1000-2900 repetitions with bandpass 150-3000 Hz. Latencies were measured from the triggering pulse to the peak of the negative deflections. Amplitude was calculated from wave peak to aftercoming trough. Our BAER normal values are very similar to those reported by Chiappa.[12]

The CA of waves III, IV, V in controls did not follow a normal Guassian distribution due to wide amplitude variability (Mean = 932 nV, SD = 221, Skewness = +1.473, Min = 650 nV, Max = 1800 nV). The Box and Cox[25] method of shifted power transformation improved but failed to fully normalize the distribution. Hence we used the non parametric methods of Mann-Whitney-Wilcoxon and Kolmogrov-Smirnov which revealed significant differences between the CA distribution of patients and controls ($P<0.01$). The lowest CA value minus 1SD was 429 nV and values below this were considered abnormal. Patients whose reponse was a combined wave IV/V were excluded from CA analysis because our control group didn't have significant numbers with this response to allow statistical comparison. Statistical analysis was performed by the SPSSX computer program except the Box and Cox method.

Results

The results of VEP testing in 217 MS patients is summarized in Table 1 and compare fairly closely with previous studies (Table 5). The response was abnormal in 39% of possible, 69% of probable and 84% of definite MS patients. In the suspect MS group ie. possible and probable combined, the overall yield was 55% positive. It is apparent that the positive yield increases proportionally to the diagnostic certainty. It is also interesting that the percentage of bilateral abnormalities increase in a similar fashion.

Table 1: VEP in 217 MS Patients Relative to Clinical Diagnosis

	Possible	Probable	Definite	Total
Patient No.	57	62	98	217
Abnormal* (%)	22 (39)	43 (69)	82 (84)	147 (68)
Bilateral Abnormal	16	29	63	108

*A response was considered abnormal if the latency in either eye was greater than 116 msec (mean +3SD), and/or the intereye latency difference was greater than 6 msec or the response was absent.

The SEP was obtained in 100 MS patients (47 definite, 26 probable and 27 possible) and the results are summarized in Table 2. The most common abnormality was an absent N19 and P/N13. Prolonged interwave latency was the next most common abnormality followed by interside latency difference of N19-EP. Absolute latency was not used in our assessment to obviate the variability produced by different arm length in the subjects. The diagnostic yield of the test in the combined possible/probable group was 45%, but rose to 79% in the definite group. Bilaterally abnormal SEP was commonly found and increased with the diagnostic certainty.

Table 2: SEP in 100 MS Patients According to Clinical Diagnosis

	Possible	Probable	Definite	Total
Patient No.	27	26	47	100
Abnormal* (%)	7 (26)	17 (65)	37 (79)	61 (61)
Bilateral Abnormal	4	7	30	41

*SEP was considered abnormal if there was:
1. Prolonged Ep-N19, Ep-P/N13 and/or P/N13-N19 interwave latencies
2. R/L interwave latency difference greater than the mean + 3SD.
3. P/N13 or N19 absent or less than 1.0 microvolts.

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BAER was obtained in 218 MS patients (99 definite, 61 probable and 58 possible) and the results summarized in Table 3. Including CA in the analysis increased the diagnostic yield in all categories by 11%. The positive diagnostic yield analyzing CCT and CA was 17%, 39% and 66% in possible, probable and definite groups respectively.

The results of CCT and CA are compared in Table 4. Individual responses from each ear were analyzed. Of 313 individual ears with normal CCT, 29 had an abnormal CA. These occurred in 25 patients. Of these 25 patients 80% had an abnormal VEP and 71% had an abnormal SEP.

Discussion

Of the three modalities, VEP is the most sensitive, confirming previous studies.[13,19,26] Chiappa[12] summarized the VEP results in 1950 patients reported in various studies and found the positive yield was 37%, 58% and 85% in the diagnostic categories of possible, probable and definite. Our yield was 39%, 69% and 84% respectively.

Others report SEP being slightly more sensitive than VEP.[14,20,27] Chiappa[12] concluded that upper limb SEP and VEP are about equal in demonstrating clinically silent lesions. In our study the sensitivity of SEP was slightly lower than VEP. Lower limb SEP may improve the diagnostic sensitivity but we did not use this technique. All agree that BAER is the least sensitive modality among the three and our study confirmed this despite using CA in the analysis.

Table 3: BAER in 218 MS Patients Relative to Clinical Diagnosis

	Possible	Probable	Definite	Total
Patient No.	58	61	99	218
Abnormal* (%)				
Excluding CA+	6 (10)	16 (31)	52 (53)	74 (34)
Abnormal (%)				
Including CA	10 (17)	24 (39)	65 (66)	99 (45)
Unilateral				
Abnormal				
Including CA	8	16	39	63

*The BAER was considered abnormal if there was:
1) prolonged central conduction time (CCT)
2) absent or very dispersed wave V or IV/V
3) low combined amplitude of waves III, IV, V
4) increased I-III interwave latency

+CA = combined amplitude

Ancillary diagnostic confirmation is most needed in the possible/probable (ie. suspected MS) group. We found the VEP abnormal in 55% of these patients; very similar to the 51% reported by Chiappa[12] who averaged the results of several studies. We also noted bilateral VEP abnormalities to increase with the degree of diagnostic certainty. The data for VEP in MS from many previous studies is similar despite varied techniques suggesting that although stimulus size, intensity and frequency have some effect on the VEP, within limits they are not of major technical importance.

Wave amplitude and amplitude ratio are of limited value in SEP analysis because of wide normal variations. Reduced amplitude, dispersion or complete absence of the response were more common than latency abnormalities in some studies.[28,29] The common SEP abnormalities reported by Chiappa[14] were absent P/N13 or N19, absent P/N13 with delayed N19 and delayed N19 with normal or increased P/N13 to N19. The commonest abnormality in our study was absent P/N13 and N19. The interesting finding was the presence of a normal N19 despite an absent wave P/N13 in some patients. Although the pathophysiology of this finding is not understood,[12] it may be an example of amplification by the central nervous system.

In our series 33% of MS patients revealed unilateral SEP abnormality which emphasizes the importance of testing each side separately. Bilateral abnormalities were more common in the definite MS patients. Our diagnostic yield in the combined possible/probable (suspected) group (45%) was comparable to other reports.

The reliability and value of BAER in identifying brainstem lesions in MS is well documented.[2,10,12,21,30,31,32,33,34] Individual ears should be tested. Overall in 63% of our patients the abnormal BAER was unilateral. Our results are compared to the other studies in Table 5. Both CA and latency were analyzed for our BAER results.

Robinson and Rudge[2] used absolute amplitude to assess abnormality of wave V but felt latency was a more reliable indicator, an observation confirmed by Stockard et al.[21] In some studies,[10,30,31] amplitude ratios of waves V, IV/V to wave I seemed more accurate than absolute peak amplitude. Most studies discouraged using absolute amplitude analysis because excessive amplitude variability in normal subjects detracts from its reliability. The difficulties in BAER interpretation are discussed by Parving et al.[35]

There are no previous studies analyzing combined amplitude of waves III, IV, V. Our study was inspired by frustration when attempting to interpret and quantitate asymmetrical amplitude responses in patients with normal latencies. We chose combined amplitude of the waves III, IV, V because these waves

Table 4: Comparison of Central Conduction Time (CCT) to Combined Amplitude (CA) According to Clinical Diagnosis

	Possible 109*		Probable 111		Definite 137	
	N1+ CA	Abn CA(%)	N1 CA	Abn CA	N1 CA	Abn CA
NL CCT	101	5 (5%)	85	11 (11%)	98	13 (12%)
Abn CCT (%)	2 (2%)	1	12 (12%)	3	19 (16%)	7

*433 "ears" in 218 patients were examined. After excluding ears with HL greater than 25dB, unmeasurable CCT due to abesnt wave I or V, and absent response, CA was compared to CCT in 357 remaining BAERS.

+NL = normal, Abn = abnormal.

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Table 5: Diagnostic Yield of VEP, SEP and BAER in Suspected* and Definite MS Patients in Previous Studies

	VEP		SEP		BAER	
	Susp.	Def.	Susp.	Def.	Susp.	Def.
Asselman et al[38]	40% (20)	84% (31)				
Lowitsch et al[1]	61% (62)	82% (73)				
Hennerici et al[39]	54% (81)	81% (16)				
Shahrokhi et al[5]	40% (89)	82% (60)				
Mastaglia et al[27]	33% (45)	83% (23)	40% (35)	94% (17)		
Clifford et al[36]	45% (31)	81% (31)	39% (28)	35% (23)		
Trojaborg et al[13]	41% (22)	96% (28)	54.5%(22)	64% (28)		
Eisen et al[29]			72% (50)	87% (30)		
Ganes[37]			58% (24)	90% (20)		
Green et al[18]	36% (11)	71% (14)	53% (15)	70% (17)	27% (15)	65% (17)
Khoshbin et al[20]	55% (49)	76% (30)	59% (48)	87% (30)	55% (49)	50% (28)
Purves et al[19]	39% (79)	91% (33)	35% (79)	67% (33)	16% (79)	45% (33)
Kjaer[16]	67% (67)	98% (58)	50% (26)	100% (3)	51% (95)	78% (78)
Chiappa et al[14]	40% (210)	81% (139)	56% (52)	68% (28)	21% (121)	47% (81)
Tackmann et al[17]	53% (32)	96% (23)	35% (31)	45% (22)	23% (31)	26% (23)
Present Study	55% (119)	84% (98)	45% (53)	79% (47)	29% (119)	67% (99)

*Although various authors used different names, all these patients fall into the possible-probable diagnostic category according to Rose.[24]

Susp. — Suspected

Def. — Definite

are thought to reflect brainstem functions and should be distorted in MS whereas waves I and II which supposedly reflect auditory nerve activity[12] should not. Of the three waves used in calculating CA, wave V was most important as it was the wave frequently affected in the abnormal responses.

Combined amplitude increased the positive yield in BAER by 4% in possible, 8% in probable and 13% in definite MS patients. The overall increase in diagnostic yield was 11%. Using CA to analyze BAER increased the diagnostic yield; however many of these patients would be identified using other evoked potential modalities. We agree with previous authors that latency and CCT are the most important parameters to measure in BAER. However, our data supports the value of CA measurement. We hope others will find this analysis useful.

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