Vestibular activation by bone conducted sound

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Objective: To examine the properties and potential clinical uses of myogenic potentials to bone conducted sound.

Methods: Myogenic potentials were recorded from normal volunteers, using bone conducted tone bursts of 7 ms duration and 250–2000 Hz frequencies delivered over the mastoid process by a 871 clinical bone vibrator. Biphasic positive-negative (p1n1) responses were recorded from both sternocleidomastoid (SCM) muscles using averaged unrectified EMG. The best location for stimulus delivery, optimum stimulus frequency, stimulus thresholds, and the effect of aging on evoked response amplitudes and thresholds were systematically examined. Subjects with specific lesions were studied. Vestibular evoked myogenic potentials (VEMP) to air conducted 0.1 ms clicks, 7 ms/250–2000 Hz tones, and forehead taps were measured for comparison.

Results: Bone conducted sound evoked short latency p1n1 responses in both SCM muscles. Ipsilateral responses occurred earlier and were usually larger. Mean (SD) p1 and n1 latencies were 13.6 (1.8) and 22.3 (1.2) ms ipsilaterally and 14.9 (2.1) and 23.7 (2.7) ms contralaterally. Stimuli of 250 Hz delivered over the mastoid process, posteroinferior to the external acoustic meatus, yielded the largest amplitude responses. Like VEMP in response to air conducted clicks and tones, p1n1 responses were absent ipsilaterally in subjects with selective vestibular neuritis and preserved in those with severe sensorineural hearing loss. However, p1n1 responses were preserved in conductive hearing loss, whereas VEMP to air conducted sound were abolished or attenuated. Bone conducted response thresholds, which measure VOR to rapid head accelerations in the plane of each semicircular canal have allowed measurement of individual canal function. Clinically useful techniques that assess otolith function, however, are few and not widely available. The click evoked myogenic potential—a relatively recently developed simple, non-invasive test of otolith function—is based on the acoustic sensitivity of the saccule.

Intense clicks delivered through headphones evoke vestibular dependent, biphasic potentials (p1n23) recordable from the sternocleidomastoid (SCM) muscles ipsilateral to the stimulated ear, during tonic activation (vestibular evoked myogenic potentials (VEMP): Colebatch et al, 1994). Their short onset latency of about 8 ms suggests that these responses are mediated by an oligosynaptic arc, which probably consists of the primary vestibular afferents synapsing at the vestibular nuclei, the second order vestibulococulocerebellar tract, and the neck motor neurons innervating the SCM. Intense short tone bursts delivered through headphones also evoke VEMP which have similar properties to those evoked by clicks when stimuli of appropriate frequency and duration are used. Both click evoked and tone burst evoked responses require the integrity of the middle ear conductive mechanism to convey the stimulus to the vestibular end organs. To enable measurement of VEMP in subjects with conductive hearing loss, Halmagyi et al proposed the use of forehead taps delivered through a modified reflex hammer, which probably results in a wave of vibration that is directly conveyed to both labyrinths, circumventing the middle ear conductive apparatus. This stimulus evokes an initial positivity (p1) followed by two negativities ("n1,n2," see fig 1), of which only the first is vestibular dependent. The precise vestibular afferents stimulated by a forehead tap have not been established, although an otolith contribution is likely, given the similarity of the waveforms to that of the click evoked response. Sheykholeslami et al recently reported that tone bursts delivered by a clinical bone vibrator applied over the mastoid process give rise to short latency potentials in the SCM, which were likely to be of vestibular origin. This new technique holds promise as an alternative to the tap evoked response, as a method of eliciting vestibular dependent responses in subjects with conductive hearing loss. It has the advantage of being a calibrated and reproducible stimulus and therefore should elicit consistent responses and enable the measurement of stimulus thresholds. The emergence of several related methods of evoking vestibulocollic reflexes necessitates assessment of their relative merits and definition of the place of each of these techniques in vestibular function testing. Our aim in the present study was to examine further the properties of responses evoked by bone conducted sound. We confirmed the vestibular dependence and defined the optimum stimulus parameters, methods of

Abbreviations: AC, air conducted; BC, bone conducted; EMG, electromyography; HL, hearing level; NHL, normal hearing level; SCM, sternocleidomastoid muscle; SPL, sound pressure level; VEMP, vestibular evoked myogenic potentials; VOR, vestibulocollic reflexes
Methods

Ten healthy adults aged 24 to 52 years (five men, five women) were studied after obtaining informed consent and local ethics committee approval.

Myogenic potentials to 7 ms/500 Hz/112 dB SPL (sound pressure level) tone bursts delivered by a clinical bone vibrator (B71, Radioear Corporation, New Eagle, Pennsylvania, USA) placed on the mastoid process (3 cm posterior to the external acoustic meatus) were recorded from all subjects. VEMP to clicks of 0.1 ms/145 dB SPL (= 100 dB normal hearing level [NHL]) and 7 ms/500 Hz tone bursts of 123.5 dB SPL delivered through headphones (our “standard parameters” for these stimuli) and forehead taps were also measured for comparison.

Figure 1: Myogenic potentials to four stimuli in a 25 year old subject. The traces consist of averaged unrectified electromyographic recordings from the left and right sternocleidomastoid muscles (SCM). The thick and thin traces represent responses ipsilateral to and contralateral to the side of stimulation, respectively. 100 dB NHl clicks delivered in the right ear evoked p1n23 responses in the ipsilateral SCM. Forehead taps produced bilateral myogenic responses (VEMP) by activating both labyrinths; these consisted of an initial positivity followed by two negativities (n1,n2), of which the first is vestibular dependent. Air conducted (AC) tones (124 dB SPL/500 Hz/7 ms), like clicks, give rise only to ipsilateral p1n1 responses. Bone conducted (BC) tones (112 dB SPL/500 Hz/7 ms) result in p1n1 responses bilaterally; the ipsilateral response being larger and occurring earlier in most subjects. Corrected reflex amplitudes for clicks, taps (averaged for left and right sides), air conducted tones, and bone conducted tones were 1.5, 2.1, 1.64, and 2.05, respectively. Tone amplitudes are plotted to scale; head acceleration is shown for taps.

Myogenic potentials evoked by bone conducted sound

Tone bursts were generated using a Jupiter 2010 function generator (Black Star, Cambridge, UK); these were amplified and gated electronically. The onset and offset of the gate were fixed and were independent of the phase of the input. Bone conducted stimuli were delivered using a B71 clinical bone vibrator previously calibrated using a Bruel and Kjaer (model BMK 4930) artificial mastoid. An initial study was undertaken using stimuli of 7 ms duration/500 Hz/112 dB SPL (“standard parameters”) delivered at three per second; these were based upon the optimum parameters for air conducted tone bursts.

To determine whether bone conducted tone burst evoked response amplitudes also increase linearly with EMG activity, responses to standard stimuli were measured in five subjects, while maintaining different degrees of background activation (approximately 20, 40, 60, 80, and 100 µV). Peak to peak amplitudes were plotted against mean rectified EMG activity. In addition, one subject was studied at 15 different levels of activation corresponding to mean rectified EMG levels of 15 µV to 150 µV. Myogenic potentials were measured in two separate experiments done seven to 10 days apart in 10 subjects to assess between-experiment reproducibility. Reproducibility of tap evoked responses was also examined for comparison.

To determine the optimum stimulus frequency, responses to 250, 500, 1000, and 2000 Hz bone conducted tone bursts were...
measured in 10 subjects. Stimuli of nearly constant intensities were used (that is, 107.5, 107, 107.5, and 105.5 dB SPL, corresponding to 20, 5, 10, and 10 volts peak to peak respectively at 250, 500, 1000, and 2000 Hz). These stimuli, generated digitally, were phase locked at 0° and had 1 ms rise and fall times and a 7 ms hold time. In each subject, the optimum stimulus frequency was determined and stimulus thresholds were measured at this frequency using 6 dB decrements in intensity.

We have previously reported clear effects of age on VEMP amplitudes and thresholds. Therefore myogenic potentials to bone conducted sound were measured in 10 older subjects aged 63 to 83 years (mean (SD), 71.6 (6.7)), using 7 ms/500 and 1000 Hz tones of 10 V p–p (equivalent to 112 and 107.5 dB SPL). These frequencies, at which the bone conductor had its greatest output, were chosen to enable more effective stimulation. Those who had no response to stimuli with these parameters were studied using more intense stimuli of 20 V p–p (115 and 112 dB at 500 and 1000 Hz). Stimulus thresholds were also measured. VEMP to air conducted tones with similar parameters were averaged and thresholds measured for comparison.

We measured responses (net potentials) to combined air and bone conducted tones delivered to the same ear at varying degrees of phase advance of the bone conducted tone, using 20° increments. Air and bone conducted tones (7 ms/500 Hz) with intensities that evoked responses of comparable amplitudes were used. The amplitude of the net potential to the combined stimuli was measured. Decreases in the net potential were interpreted as evidence of phase cancellation of the stimuli.

**Patients with specific lesions**

Responses to clicks (145 dB SPL) and to air and bone conducted tones with the standard parameters were measured in four subjects who had undergone selective unilateral vestibular neurectomy, in six subjects with conductive hearing loss (“air–bone gaps” of 10–40 dB), and in four subjects with profound sensorineural hearing loss (“air–bone gaps” of 10–40 dB), and in four subjects with superior semicircular canal dehiscence had stimulus thresholds measured to clicks, air conducted tones, and bone conducted tones. One subject with a bilateral near total vestibulopathy, who had undergone selective unilateral vestibular neurectomy as a treatment for intractable vertigo had absent short latency bone conducted responses in the ipsilateral ear.

**VEMP evoked by air conducted clicks, tones, and forehead taps**

VEMP to clicks and tone bursts delivered through headphones were measured in all 10 subjects. The clicks of 0.1 ms duration and 145 dB SPL (= 100 dB NHL) were generated using an ST 10 evoked potential stimulator (Medelec, Surrey, UK) and tone bursts of 2 V p–p intensity = (123, 123, 124, and 125 dB SPL at 250, 500, 1000, and 2000 Hz) were generated using the function generator. During each recording, stimuli were presented pseudorandomly in each ear at five per second through calibrated headphones (TDH 49, Telephonics Corp, New York, USA) and responses to 512 stimuli (256 in each ear) were averaged. Frequency tuning properties of air conducted tones were examined using the same methods as for bone conducted tones. Click and air conducted tone thresholds were measured using 5 dB and 6 dB decrements, respectively.

Forehead taps were delivered manually through a small gauze pad placed approximately over Fpz, using a nylon handled reflex hammer fitted with an inertial trigger switch. Responses to 64 stimuli were averaged. In subjects who did not have two separate negative peaks (n1,n2), a slur on the upstroke leading to the negativity or a point at which a clear change in the slope of the upstroke occurred was marked as n1. Data of subjects who had “non-separating peaks” without these features were treated as missing values.

**Statistical methods**

SPSS version 9 (SPSS Inc, Chicago, Illinois, USA) was used for all data analyses. To examine the effects of varying location and frequency, repeated measures analysis of variance (ANOVA) with contrasts were done using the corrected reflex amplitudes as the dependent variables and stimulus location or stimulus frequency as fixed factors. A significance level of 0.05 was used, with Bonferroni corrections for multiple comparisons. All results are given as mean (SD) unless otherwise noted.

**RESULTS**

**Properties of bone conducted responses and comparison with VEMP to other stimuli**

All 10 subjects had short latency biphasic positive-negative (p1n1) responses to bone conducted tone bursts of standard parameters, which were present bilaterally. Later responses were also present but will not be discussed further. Eight subjects had larger amplitude bone conducted responses recorded from the SCM ipsilateral to the stimulus and smaller ones from the contralateral SCM (see fig 1) and the reverse. All subjects had VEMP to clicks and “air conducted” tone bursts of standard parameters recorded from the SCM ipsilateral to the side of stimulation. Seven of the 10 subjects had measurable VEMP to forehead taps recorded from both SCM, two had measurable VEMP on one side (SCM) only. There were four “non-separating” responses (two unilateral and one bilateral).

Bone conducted tones evoked myogenic responses, which had significantly higher average corrected amplitudes (mean (SD), 1.36 (0.45)) recorded from the SCM ipsilateral to the stimulus compared with the contralateral SCM (0.93 (0.66)) (p < 0.001). Raw amplitudes were 77.0 (26.2) µV ipsilaterally and 55.2 (34.8) µV contralaterally. Peak latencies recorded from the SCM ipsilateral to the stimulus occurred earlier (average p1 and n1 of 13.6 (1.8) ms and 22.3 (1.2) ms) compared with those recorded over the contralateral SCM (p1 and n1 of 14.9 (2.1) and 23.7 (2.7) ms). The range for p1 latencies was 11.9 to 16.5 ms ipsilaterally and 12.5 to 19.6 ms contralaterally, and that for n1 latencies was 20.0 to 26.6 ms ipsilaterally and 20.1 to 30.2 ms contralaterally.

The average corrected amplitudes for click, tap, and air conducted tone burst evoked responses were 1.98 (0.48), 2.4 (0.52), and 1.3 (0.52) µV (raw amplitudes of 130.4 (32.9), 247.0 (61.2), and 78.3 (32.8) µV respectively). The average peak latencies (p1n23 or p1n1) for clicks, taps, and air conducted tones were similar to those reported in previous studies (12.4 (1.2) ms and 20.6 (1.3) ms for clicks; 9.7 (1.2) ms and 18.2 (1.6) ms for taps; and 14.3 (1.3) and 22.9 (1.7) ms for 500 Hz air conducted tones).

Three of the four subjects who had undergone selective vestibular neurectomy were generated as a treatment for intractable vertigo had absent short latency bone conducted responses in the ipsilateral SCM on stimulation of the mastoid on the side of the lesion. On stimulation of the intact side, p1n1 responses were present on that same side only. One of these three subjects, when stimulated over the operated side, had no response ipsilaterally but a well formed p1n1 response was recorded from the contralateral SCM, presumably due to bone conduction of the tone to the opposite labyrinth (fig 2). A fourth subject who had undergone selective vestibular neurectomy had a small p1n1 response recorded from the ipsilateral SCM following stimulation of the side of the lesion, but this finding was not reproducible on repeated recordings. The subject was also found to have residual posterior semicircular canal function on impulsive testing, suggesting residual nerve function related to the inferior division of the vestibular nerve (Cremer...
P, personal communication). As with click and tone burst evoked VEMP, short latency responses to bone conducted sound were preserved in the four subjects with severe sensorineural hearing loss. The above findings confirm the conclusions of Sheykholeslami et al., that short latency p1n1 myogenic responses to bone conducted sound are vestibular dependent and we shall henceforth refer to them as “bone conducted VEMP”.

All five subjects tested for the effect of stimulus location had bone conducted VEMP to the standard stimulus parameters when the bone conductor was placed on the mastoid process (3 cm posterior to the external acoustic meatus). When stimulated over the temporal and occipital regions, ipsilateral bone conducted VEMP were obtainable only in three and two of the five subjects, respectively. Stimulation over Fpz resulted in bilateral responses in three of the five subjects, a unilateral response in one, and absent responses in the other. The average corrected VEMP amplitudes for the mastoid, frontal, anterior temporal, and occipital regions were 1.22, 0.32, 0.36, and 0.31, respectively. Raw amplitudes were 76.0, 44.0, 14.0, and 6.5 µV, respectively. Upon detailed mapping of amplitudes, when the stimulus was applied at 12 different locations in relation to the external acoustic meatus, larger bone conducted VEMP were recorded from locations superior and posterior to the meatus (fig 3). A location 3 cm behind and 2 cm above the external acoustic meatus yielded the highest average VEMP amplitude for the 10 subjects, although the best site varied between subjects. A significant effect of location was present on ANOVA ($F_{11, 99} = 16.5$, $p < 0.001$). On simple contrasts between VEMP amplitudes at the optimum location and the remaining sites, there were significant differences between it and eight of the remaining 11 locations. There were no significant differences between the amplitude at the optimum site and those at three other locations (“optimum locations”). These formed an inverted L behind and above the external acoustic meatus and were located 3 cm behind, 3 cm behind and 2 cm above, 3 cm behind and 4 cm above, and 4 cm directly above the external acoustic meatus, respectively (fig 3).

The peak to peak amplitudes of bone conducted VEMP increased linearly with increasing mean rectified EMG activity.
Correlation coefficients ($r$) between SCM activation and peak to peak amplitudes in the same subject ranged from 0.9 to 0.99. In the subject who was tested at 15 different levels of background activation (18 to 155 $\mu$V), the raw peak to peak amplitudes varied from 21.1 to 262 $\mu$V (12-fold). The corrected amplitudes only varied from 1.1 to 1.9 (1.7-fold), confirming that this measure was more constant and less likely to be influenced by EMG activity when compared with raw amplitudes. Correlation of VEMP amplitudes to the standard stimulus obtained on two separate days (approximately one week apart) for 10 subjects resulted in a coefficient of 0.77 ($p < 0.001$) for bone conducted VEMP ($n = 10$). A similar correlation coefficient (0.71) was obtained for tap evoked responses ($n = 10$). The tendency to have larger VEMP recorded from the contralateral SCM, observed in two subjects, was not reproducible between experiments.

Frequency tuning properties and side to side differences

Average corrected VEMP amplitudes recorded from the ipsilateral SCM for 7 ms/250, 500, 1000, and 2000 Hz bone conducted tones (107 dB nominally) were 1.43 (0.2), 0.68 (0.2), 0.88 (0.2), and 0.30 (0.1), respectively (fig 5). Average raw amplitudes were 104.4 (60.2), 58.1 (54.7), 70.2 (47.0), and 24.1 (15.9) $\mu$V, respectively. Differences between reflex amplitudes measured at the four stimulus frequencies were much greater than the slight differences in stimulus intensity for each frequency (see Methods). In contrast to air conducted tones (fig 5), the largest response was at 250 Hz. On ANOVA with contrasts, average VEMP amplitudes in response to the 250 Hz stimulus were significantly higher than average amplitudes obtained with the other three stimuli ($F_{3,27} = 41.64$, $p < 0.001$). There was no significant difference between responses to 500 and 1000 Hz stimuli ($p = 0.56$). The optimum stimulus frequency was 250 Hz for 17 sides and 1000 Hz for three sides. Mean thresholds for bone conducted tones were 97.5 (3.9) dB SPL (30.5 dB HL (hearing level)) when measured using the 250 Hz stimulus and 100.3 (5.0) dB SPL (42.3 dB HL) using a 500 Hz stimulus. Thresholds for clicks and air conducted tones were significantly higher at 131.7 (4.9) dB SPL (86.7 dB NHL) and 114 (5.3) dB SPL (106 dB HL), respectively (fig 6).

Asymmetry ratios for bone conducted tones were calculated using the VEMP amplitudes recorded from the SCM ipsilateral to the stimulus. The average asymmetry ratios for bone conducted tones were 17.3% (range 0 to 58.2), 38.5% (0 to 775

Figure 4

The effect of background electromyographic (EMG) activity on bone conducted vestibular evoked myogenic potential (VEMP) amplitudes. The traces are averaged unrectified EMG recorded from the right sternocleidomastoid (SCM) of one subject during different degrees of activation in response to a 112 dB SPL (10 V p-p)/500 Hz/7 ms bone conducted tone delivered to the right mastoid process. The mean rectified EMG activity level for the 20 ms preceding the stimulus is given on the left side, next to the raw traces. Peak to peak amplitudes rise linearly with background activation ($r=0.92$).

Figure 5

Frequency tuning properties of air and bone conducted tone burst evoked responses. Mean and SEM values of vestibular evoked myogenic potential (VEMP) amplitudes in response to 7 ms tone bursts of 250, 500, 1000, and 2000 Hz are given; the lines connect average amplitudes at the four frequencies. The thin line represents VEMP to air conducted tone bursts of 123 to 125 dB SPL and the thick line, VEMP to 105.5 to 107.5 dB bone conducted tone bursts. Air conducted tones have a tuning curve that peaks between 500 and 1000 Hz with marked reduction of mean VEMP amplitudes at 250 Hz. Bone conducted VEMP, in contrast, have maximal amplitudes at 250 Hz.
42.8). VEMP to clicks and taps were 5.4% (0 to 14.4) and 21.1% (0 to 500 to 2000 Hz frequencies. The mean asymmetry ratios for palpate had absent bone conducted VEMP to all but the 250 Hz stimulus (at an intensity of 107 dB), and this was responsi- for the range of asymmetry ratios obtained for the 500 to 2000 Hz frequencies. The mean asymmetry ratios for VEMP to clicks and taps were 5.4% (0 to 14.4) and 21.1% (0 to 42.8).

In the 10 older subjects tested (20 ears), six sides had absent VEMP to 500 Hz and 1000 Hz bone conducted stimuli of 10 V peak to peak (equivalent to 112 and 107.5 dB SPL, respectively). All these had detectable VEMP when the stimu- lus was increased to 20V peak to peak (115 and 112 dB at 500 Hz and 1 kHz, respectively). VEMP to air conducted tones were absent in seven and five ears at frequencies of 500 and 1000 Hz, respectively. None of these subjects had conductive hearing loss on audiometric testing. Stimulus thresholds at 500 Hz were 108.6 (4.6) dB SPL (50.6 dB HL) for bone conducted VEMP (n = 20 ears) and 121.5 (2.9) dB SPL (113.5 dB HL) for air conducted tones (n = 15 ears), both of which were significantly higher than the thresholds obtained in the 10 younger subjects using 500 Hz stimuli (p < 0.001 in both cases).

We were able to demonstrate modest phase cancellation between air and bone conducted tone burst evoked responses. For the three subjects tested, average reflex amplitudes to the air conducted stimulus alone, bone conducted sound alone, and the maximum net potential obtained with the combined stimulus were 1.01, 1.06, and 2.38, respectively. Thus the maximum net potential approximated the sum of the amplitudes of the “net potentials” of three subjects stimulated by air and bone conducted thresholds of 95 to 107.5 dB SPL at 500 Hz. The click thresholds for subjects with the Tullio phenomenon were 105 to 110 dB SPL and air and bone conducted thresholds were 88 to 94 dB SPL and 83 to 95 dB SPL, respectively. While the click and air conducted tone thresholds in Tullio subjects were at least 10 dB below the lowest normal threshold, those for bone conducted tones approached normal levels in two of the five ears tested.

Subjects with specific lesions
Six subjects with conductive hearing loss (eight affected ears) had absent VEMP to 145 dB SPL clicks and air conducted tone bursts of standard parameters on the affected sides. In contrast, VEMP to bone conducted tones of 115 dB/500 Hz/7 ms were present for in all affected ears.

Four subjects (five ears) with the Tullio phenomenon had average thresholds of 107 dB SPL (62 dB NHL) to clicks, 90.4 dB SPL (82.4 dB HL), to air conducted tones, and 90.2 dB SPL (32.2 dB HL) to bone conducted tones, all significantly lower than those of normal subjects (p < 0.001). The average reduction in thresholds from normal values was 24.7, 23.6, and 10.1 dB for air conducted clicks and tones and bone con- conducted tones, respectively (fig 6).

The subject with markedly reduced caloric responses binaurally (maximum SPV on stimulation of either side = 2°/s) as well as marked reduction of VOR to head impulses in the planes of all three semicircular canals on each side, had pres- ervation of VEMP to clicks, air conducted tone bursts, and bone conducted tone bursts of standard parameters delivered to the right side, with corrected amplitudes of 0.97, 1.43, and 0.76 and raw amplitudes of 52.5, 44.9, and 45.1 µV, respectively. Upon stimulation of the left ear, VEMP to clicks were absent, and responses to air and bone conducted tones were markedly reduced, with corrected amplitudes of 0.37 and 0.42 and raw amplitudes of 23.8 and 67.0 µV, respectively.

DISCUSSION
Although head rotation and acceleration are the adequate physiological stimuli for the vestibular apparatus, non- mechanical stimuli such as loud sound, vibration, and galvanic currents activate primary vestibular afferents and have been used to evoke VEMP. Vestibular responses to sound have been attributed to stimulation of the saccule, which in other species such as fish and amphibians serves as a primary or secondary organ of hearing.12-14 Recordings from primary and secondary vestibular neurones in guinea pigs and cats in response to intense clicks or tones have shown increases in neural discharge.14-16 Using labelling techniques and responses to physiological stimuli, acoustically responsive afferents been traced to the saccule.17 The vestibular apparatus is sensitive to vibration in amphibians18 and mammals.19-22 In
ears tested. Similar optimum frequencies have been reported for bone conducted VEMP was 250 Hz for most of the subjects. More recently, low frequency (100 Hz) vibration of the mastoid process has been found to evoke nystagmus (beating away from the side of the lesion) and shift of the subjective visual horizontal (towards the lesion) in subjects with unilateral vestibular hypofunction, which may reflect asymmetrical vestibular activation.

Bone conducted sound of 7 ms/500 Hz/112 dB SPL produced short latency p1n1 potentials in all 10 normal subjects aged 24 to 52 years, reactions which were abolished following selective vestibular neurectomy, and preserved despite profound sensorineural hearing loss, and therefore appear to be another form of VEMP. Later responses, sometimes present, were not abolished by vestibular nerve section. Unlike VEMP to clicks and air conducted tones, bone conducted VEMP were often bilateral. Most subjects had larger bone conducted VEMP thresholds than peak latencies (p1 and n1 ranging between 11.9 and 16.5 ms and between 29.4 and 26.6 ms) recorded from the ipsilateral SCM and smaller ones with average peak latencies occurring about 1 ms later contralaterally (p1 and n1 ranging between 12.5 and 19.6 ms and between 20.1 and 30.2 ms). Bone vibration spreads widely throughout the skull, and the contralateral bone conducted VEMP are likely to be responses arising from the opposite labyrinth following stimulus conduction across the skull. Although crossed neural pathways are known to exist, contralateral bone conducted VEMP clearly differ from the “n1p1” crossed neural responses to galvanic stimulation, which are of opposite polarity (negative–positive responses) and also have earlier peak latencies compared with the ipsilateral response. The findings in the subject with selective vestibular nerve section indicate that “crossed” bone conducted VEMP do not depend upon activation of the ipsilateral vestibular apparatus. The larger bone conducted VEMP recorded from the contralateral SCM in two subjects further illustrate the vagaries of sound transmission by bone conduction. Similar observations have been made for hearing. Bone conducted sound delivered through the mastoid process has been shown, owing to the asymmetry of skull thickness, to stimulate the contralateral cochlea more effectively in some subjects. The optimum stimulus frequency for bone conducted VEMP was 250 Hz for most of the cars tested. Similar optimum frequencies have been reported by Sheykholeslami et al. Differences between air and bone conducted tones are likely to relate to the different filtering properties of bone and the middle ear as well as to potential differences in the mechanism and specific site of action of the two stimuli. As the B71 vibrator did not permit delivery and accurate calibration of tones of less than 250 Hz frequency, we were unable to define the tuning curve fully.

While VEMP to air conducted sound are thought to be of saccular origin, the precise origin of the afferents responsible for the bone conducted VEMP is not yet known. Previous experiments which achieved phase cancellation of an air conducted sound by a bone conducted sound demonstrated that the two stimuli activate cochlear receptors by similar mechanisms. We have shown that the bone conducted VEMP is vestibular dependent and has similar latency and waveform to the VEMP evoked by air tone bursts. Results obtained from the patient with markedly attenuated canal function imply that bone conducted VEMP arise from the otolith organs. Partial cancellation of responses when air and bone conducted tones were delivered out of phase is consistent with overlap in the afferents stimulated by the bone stimulus. The findings indicate that the receptors responsible for bone conducted responses arise from the otoliths and in part, at least, from the saccule.

Stimulation over the mastoid yielded bone conducted VEMP more consistently compared with fronto and occipital bone. The results are better at the external auditory meatus. Auditory studies comparing bone conduction thresholds over the frontal bones and mastoid report lower thresholds over the mastoid. Studies in humans comparing BAER latencies with the stimulus over the frontal, occipital, and temporal bones have reported earlier wave V latencies to temporal stimulation. Our optimum location for stimulus delivery occurred almost always in one of the four locations forming an inverted “L” shape posterior and superior to the external acoustic meatus; other locations near the meatus give smaller responses. Sohmer and Freeman reported shorter BAER latencies when the bone vibrator was placed anterior to the external acoustic meatus over the thinnest part of the temporal bone. We did not find bone conducted VEMP amplitudes to be significantly larger anterior to the external acoustic meatus. This may reflect the more posterior location of the vestibular apparatus compared with the cochlea. Our results indicate that effective stimulation can be delivered at any one of the four optimal locations providing the bone conduction makes good mechanical contact. Symmetrical sites should be used to minimise differences in amplitude between sides.

The perceived loudness of sounds is a function of the middle ear, the cochlea, and the central neural pathways. The standard measure of this property, for continuous sound, is expressed as dB HL (hearing level) and the relation between dB HL and dB SPL (sound pressure level) differs with frequency. The HL reference is not appropriate when the cochlea is not the organ being stimulated by sound, as is the case for VEMP. The reference levels for air and bone conducted sound (0 dB) are defined differently. For sound in air, 0 dB SPL is defined as a pressure (20 µPa), for bone conduction 0 dB SPL is defined as a force (1 µN). The different reference levels prevents direct comparison of air and bone conducted sound. If force is used for comparison, 0 dB for air is substantially less than 1 µN. At 1 kHz, 0 dB HL (for sound in air) is close to 0 dB SPL, implying an extraordinary level of sensitivity, close to the physical limits of detection. Contrasting with sound in air, 0 dB HL for continuous bone conducted sound is 42.5 dB higher than the SPL reference for 1 kHz (and therefore approximately 130 times less sensitive). von Békésy argued that this reduced sensitivity is a desirable characteristic that is in part a consequence of the structure of the cochlea.

The stimulus threshold for air conducted VEMP was 114 dB SPL = 106 dB HL, and that for bone conducted VEMP 97.5 dB SPL = 30.5 dB HL at 250 Hz (using standard HL thresholds). The difference between hearing thresholds and VEMP thresholds is much larger for air conducted sound than for bone vibration. Bone vibration at a given perceptual intensity is therefore a more effective vestibular stimulus than air conducted sound, implying a relatively greater sensitivity of the vestibular apparatus to bone conducted sound when compared with the cochlea. Subjects with sound induced vestibular symptoms—the Tullio phenomenon—have a low stimulus threshold for VEMP to air conducted clicks, and this has been attributed to an increased sensitivity of the vestibular apparatus to sound at the receptor level, as neural excitability has been shown to be normal in these subjects. Bone conducted VEMP thresholds, although still significantly lower than those of normal subjects, were not as markedly reduced as the thresholds of VEMP to air conducted clicks in the six subjects with the Tullio phenomenon. A significant proportion of “bone conduction” does in fact travel through the middle ear so that some reduction in bone conducted VEMP thresholds would therefore be expected. The vestibular receptors themselves appear to be normal; thus the component of vestibular activation caused by a direct effect on the receptors by distal stimulation and the inherent effects on the otoliths may be unaltered, leading to lesser abnormalities than occur with air conducted sound.

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The clinical indications for the use of bone conducted VEMP are similar to those for taps, and they have a similar reproducibility, but they are more consistently present in normal subjects and can be calibrated. Bone conducted VEMP are therefore a suitable alternative to the tap VEMP but they do not replace click evoked VEMP which are more symmetrical, are highly reproducible (r = 0.9) between experiments,7 and have a wider separation between normal thresholds and those of subjects with the Tullio phenomenon. All subjects with absent click evoked responses should be tested for VEMP to either bone conducted tones or taps to exclude conductive hearing loss as the cause. When compared with air conducted sound, larger bone conducted stimuli may be safely used, as they do not stimulate the cochlea as effectively. This technique may also be useful in studying older subjects with higher stimulus thresholds.7 Absent VEMP to both air and bone conducted sound suggest a lesion along the vestibulocollic reflex pathway. Measurement of VEMP to transmastoid galvanic stimulation11 may yield useful information in this context, as this stimulus acts upon the terminal part of the primary vestibular afferents. The preservation of a response to galvanic stimulation when sound evoked responses are absent makes a lesion of the vestibular end organ most likely.7

Conclusions

Bone conducted sound evokes VEMP that provide an additional measure of vestibular function, which is not confounded by conductive hearing loss. They complement information obtained from click VEMP and other techniques currently used in vestibular assessment.

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Remission of progressive multifocal leucoencephalopathy in SLE after treatment with cidofovir: a 4 year follow up

Progressive multifocal leucoencephalopathy (PML) is an opportunistic infection caused by human polyomaviruses such as the JC virus. It usually occurs as a severe complication of immunosuppression in patients with primary disorders of the immune system or secondary impairment of immune function, for example, after iatrogenic states of immunosuppression. PML usually takes a rapidly progressive course and advances to death within 1 to 18 months. Today, PML is mainly seen in AIDS, while previously it was typically found in patients with granulomatous, neoplastic, or infectious diseases. In granulomatous diseases particularly, PML is thought to occur as a result of iatrogenic states of immunosuppression, but it is also seen in patients aggressively treated with immunosuppressive therapy for systemic lupus erythematosus (SLE). PML progresses to death in most of these patients even after withdrawing immunosuppressive therapy. Therefore additional therapy, aimed at supporting a more rapid restoration of immune function, was warranted.

Case report

We report a 40 year old woman diagnosed with SLE at the age of 20 years, based on four American College of Rheumatology criteria (erythema, arthritis, elevated antinuclear antibodies, and anti-dsDNA antibodies). Owing to neuropsychiatric lupus (the patient had experienced several psychotic episodes) with suspected vasculitic changes on cerebral magnetic resonance imaging (MRI), the patient had undergone 12 cycles of cyclophosphamide pulse therapy in 1995/96 followed by immunosuppressive treatment with mycophenolate mofetil in 1998, and azathioprine in 1999. Follow up cerebral MRI scans at that time were normal.

In January 2001, she again developed psychotic episodes and an initially mild ataxia. She had repeatedly been put on low doses of corticoids but on no other immunosuppressive therapy during the previous 2 years. MRI revealed a lesion in the left cerebellum, which was hyperintense on T2 and hypointense on T1 weighted images. No lesions were seen in the cerebral hemispheres. Central nervous system manifestation of SLE was suspected, although the patient revealed only moderate signs of SLE activity (elevated anti-dsDNA antibodies, slightly decreased complement levels C3c and C4, increased erythrocyte sedimentation rate, but normal C reactive protein). There were no signs of severe immunosuppression; laboratory data showed normal levels of immunoglobulins and only slightly decreased lymphocytes, especially CD8+ T lymphocytes. The patient received two pulses of cyclophosphamide and high doses of corticosteroids to reduce the presumed cerebral SLE activity. In addition, she received antipsychotic medication.

While the psychosis was readily controlled by this treatment, the patient deteriorated neurologically. She developed a severe, disabling, rapidly progressive, left sided hemi-ataxia and was unable to walk. A control MRI of the brain in February 2001 revealed a progression of the lesion in the left cerebellum and a new lesion in the middle cerebellar peduncle. The lesions again presented as hyperintense on T2 and hypointense on T1 weighted images (fig 1A). Owing to the neurological deterioration after initiation of immunosuppression and the presentation of the lesions on MRI, PML was considered as a differential diagnosis. PCR revealed JC virus DNA in the cerebrospinal fluid (CSF). As cerebral SLE and PML require an intense but divergent therapy, a brain biopsy was obtained from the cerebellar lesion. Histopathology confirmed the diagnosis of PML. HIV tests were negative, T cell counts were normal, and signs of malignancy were lacking. Immunosuppression was discontinued. Because PML is usually lethal in patients with SLE even after omission of immunosuppression, we considered options for an active antiviral therapy. There was evidence from several reports in AIDS patients that cidofovir, an inhibitor of viral DNA polymerase, may reduce the size of PML lesions and thus prolong survival. Lacking therapeutic alternatives we therefore administered intravenous cidofovir (5 mg/kg body weight) at initially bi-weekly intervals, after obtaining informed consent. After the third and fourth cycle, the patient improved dramatically. She was able to walk again and only showed a mild residual ataxia. MRI revealed reduction of the lesions in the cerebellum and middle cerebellar peduncle with no new sites of active disease (fig 1B). PCR for JC virus DNA in the CSF was now negative. The treatment with cidofovir was continued with longer intervals (8–12 weeks). The therapy was generally well tolerated. After the fifth cycle, mildly increased creatinine levels were found. After one cycle with 4 mg cidofovir/kg body weight, kidney function was quickly normalised and the following cycles could be administered at the initial dosage. Fourteen months after initiation of the treatment, the patient had completed the 10th cycle of therapy with no signs of disease activity. MRI scans of the brain showed further regression of the lesion with no signs of progression.

Figure 1 T2 weighted MRIs showed (A) extended white matter lesions in the middle cerebellar peduncle and left cerebellum, February 2001; (B) regression of the lesions after four cycles of cidofovir, July 2001; and (C) further regression with residual gliotic lesions, July 2004.
active inflammation (not shown), and cidofovir treatment was discontinued. At present, (4 years follow up after the first treatment and 2.5 years after the last cycle of cidofovir), the patient still shows no signs of disease activity. CSF PCR for JC virus DNA remains negative, and a recent MRI scan of the brain was unchanged (fig 1C). As of March 2005, the patient lives at home, is able to walk, and is independent.

Discussion

We report a patient with SLE who survived PML after treatment with cidofovir and discontinuation of immunosuppression. First evidence for possible efficacy of cidofovir in the treatment of PML in a patient with SLE was presented in a case report.1 Discontinuation of immunosuppression and treatment with cidofovir resulted in reversal of JC virus positivity and stabilisation of MRI lesions. However, the patient died due to serious kidney failure.

It remains unclear whether the improvement in both patients was induced or supported by cidofovir or whether it could have been acquired by discontinuation of immunosuppression alone. However, patients with PML in SLE usually die after discontinuation of immunosuppression alone.1-3 Interestingly, our patient did not show signs of severe immunosuppression at the point of manifestation of PML. These observations may suggest a predisposition of patients with SLE to PML that may not be explained by their immunosuppression alone.

We conclude that cidofovir should be offered to SLE patients developing PML due to immunosuppression in addition to withdrawal of immunosuppressive therapy, as death is likely without antiviral therapy. Cidofovir may be effective against PML caused by non-AIDS related states of immunosuppression.

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References


Dramatic improvement in non-AIDS related progressive multifocal leuкоencephalo-pathy

Progressive multifocal leuкоencephalo-pathy (PML) is a rare disorder occurring when a strain of papovavirus (JC virus) infects the central nervous system. It results in a generally quick and fatal outcome. It is associated with cell mediated immune deficiency diseases but some few cases were reported in immunocompetent hosts. Since 1981, it has been commonly associated with AIDS. In AIDS-related PML, a long term survival without real neurological improvement has been reported in patients treated with highly active antiretroviral therapy (HAART). Few cases of improvement with cidofovir or aracytine have been described in AIDS related or non-AIDS related PML,1-3 but in larger trials in AIDS related PML, no clinical benefit was found.1 As a whole, the treatment of this progressive demyelinating disease remains controversial, in particular in the rare cases of non-AIDS related PML. We describe a patient with an underlying haematological disease, without clear cut immune cell deficiency, who developed rapidly progressive PML. The patient showed clinical, virological, and imaging improvement when treated with an association of intravenous and intrathecal cytosine arabinoside combined with intravenous cidofovir.

A 48 year old man presented with progressive multiple lymphadenopathies, hepatosplenomegaly, weight loss, and blood cell count abnormalities. Fine needle aspiration cytology of lymphadenopathy diagnosed marginal zone B cell lymphoma. There was also bone marrow and blood proliferation. A few weeks after the diagnosis, the patient noticed rotatory vertigo and visual problems suggestive of a right homonymous hemianopia. Because of dissemination and the large tumour mass, chemotherapy (CHOP: cyclophosphamide, doxorubicin, vincristine and prednisone) was started one month after the onset of neurological symptoms. Following the first course of chemotherapy, his neurological symptoms worsened, and language disorders appeared. No real immunodeficiency was shown—the absolute CD4+ count was 549/mm³ (normal 5–12). The patient was HIV and HTLV-1 seronegative. Cerebral magnetic resonance imaging showed a non-contrast-enhancing lesion in the left occipital white matter (fig 1A).

Cerebrospinal fluid (CSF) analysis was normal apart from a moderate increase in CSF protein (0.7 g/l). Susception of PML was confirmed by a positive polymerase chain reaction (PCR) for JC virus DNA. Chemotherapy was discontinued but neurological symptoms worsened rapidly and the patient developed a right hemiplegia, global aphasia, alexia and agraphia, apraxia, and cortical blindness concurrently with MRI deterioration (fig 1H).

Three months after his first symptoms, treatment was started with intravenous aracytine 2 mg/kg/d for five days every three weeks, combined with intrathecal aracytine (30 mg) weekly and intravenous cidofovir 5 mg/kg/d once every two weeks. The main adverse effect of this treatment was grade IV bone marrow toxicity, inducing spacing in the rhythm of treatment administration. One week after treatment onset, the patient stabilised and after one month began improving. After three months, he had recovered completely from his hemiplegia, and had significant improvement in his aphasia and cortical blindness. Right hemianopia and minor alexia without agraphia persisted. This dramatic improvement was confirmed by cerebral imaging, by the absence of JC virus DNA detection in CSF, and by a specific reaction of CD+ T cells against JC virus. We decided to continue subcutaneous aracytine 2 mg/kg/d for five days monthly and intravenous cidofovir twice weekly. Fifteen months after treatment onset, the patient was still ambulatory and cerebral imaging showed no increase to improve (fig 1C). Lymphoma tumour burden did not clearly change during the treatment.

Comment

We report the favourable outcome of a patient with non-AIDS-related PML treated with a combination of intravenous and intrathecal aracytine and cidofovir. As the patient was not immunocompromised and had not received immunosuppressive treatment at PML onset, risk factors for the occurrence of PML are unclear. Treatment led to a rapid clinical and radiological improvement which was long lasting despite treatment delay and the patient’s worrying clinical condition at treatment onset. Dose and administration schedules of cytarabine and cidofovir were derived from reports suggesting individual beneficial effects of these drugs.1-3 To our knowledge, these drugs have not been used in combination before. In comparison with previous reports, the present case suggests a more rapid and prolonged effect of this therapeutic combination than with either aracytine or cidofovir treatment alone. This efficacy may be explained by a synergy between the drugs and by their different routes of administration. We thought that the improvement in our patient was related to the treatment because there was a temporal link with treatment onset and because of the radiological features. In cases of PML stabilising without specific treatment have usually been associated with an inflammatory response to the virus, indicated by contrast enhancement on imaging). The main limiting factor of this treatment was bone marrow toxicity. During the periods of immune deficiency, the patient’s neurological condition did not deteriorate, suggesting that PML occurrence in this patient was linked to a qualitative defect of cells rather than to their absolute count. Immunological studies have shown that JCV specific CD4-T cell responses play a
major role in the control of PML development; for example, in one study no specific T cell response was demonstrated in a series of 14 patients before treatment, whereas nine of 10 survivors recovered specific immunity. Our patient thus probably had no specific T cell response against JCV before treatment, but recovered a moderate but significant response while on treatment, possibly explaining PML regression. Such a restoration of T cell response can be achieved by HAART in AIDS. This observation suggests that the combination of aracytine and cidofovir could have had a similar action in restoring a specific T cell response against JCV in our patient. A direct effect of these nucleosidic analogues against JC Virus DNA may also explain the rapid clinical and radiological improvement in our patient. Despite its substantial bone marrow toxicity, this observation suggests that the new association of intrathecal and intravenous aracytine with intravenous cidofovir could be useful in patients with PML, particularly those with an underlying haematological disease. It is worth noting that bone marrow toxicity did not lead to deterioration of the neurological status of the patient, supporting the view that a specific action in restoring a specific T cell response against JCV in our patient warrants further prospective studies testing this drug combination.

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Diaphragmatic paralysis and respiratory failure as a complication of Lyme disease

There have been five recorded cases of diaphragmatic paralysis as a complication of neuroborreliosis. Here we report another case of Lyme meningoradiculitis, caused by an identified tick, leading to bilateral diaphragmatic paralysis with an abbreviated course on treatment.

Case report
A 59 year old female presented with a recent history of abdominal pain and falls because of a weakness in her right leg. She had been complaining of flu-like symptoms with twitches in her back and pain in her right side for a month. She gave a history of recently having been bitten by ticks whilst gardening. There was no history of any recent rash. On the day of presentation, she complained of a mild cough, reduced appetite, abdominal distension, constipation, and dysuria. She was a lifelong smoker but was generally healthy.

At presentation her blood pressure was 210/107 mm Hg. There was tenderness of her epigastrium. She had bruising on her right leg that she associated with the falls.

The chest radiograph on admission was unremarkable. Abdominal x ray showed dilated loops of small bowel and a loaded colon. Her only blood abnormality was hyponatraemia at 121 mmol/l. She was admitted for further investigations.

On day 3 of admission she became increasingly short of breath and on examination had decreased basal air entry. On day 4 her respiratory rate was 25/min and arterial blood gases (ABG) demonstrated hypoxaemia but adequate ventilation with pH 7.51, Po2 6.7 kPa, and Pco2 4.7 kPa. Her chest radiograph showed left basal changes. On day 5 her Pco2 had risen to 6.8; she was admitted to the intensive care unit and non-invasive ventilatory support was commenced. She had a decreased inspiratory pressure and a decreased vital capacity. She was noted to have absent gag reflex and poor swallow and on day 6 was intubated to protect against aspiration pneumonia. The patient remained fully conscious and co-operative, easily triggering the ventilator but requiring significant inspiratory pressure support of 20 cm H2O.

Neurological examination demonstrated right hip and knee extensor weakness (2/5), absent right knee jerk, and a loss of sensation over her upper abdomen that was removed and on closer examination was identified as tick mouthparts (fig 1).
In all previous cases of diaphragmatic palsy as a complication of Lyme disease, either the patient reported dyspnoea or hypoxia was noted on ABG. The diagnosis of phrenic nerve palsy was made by the following methods: hemidiaphragm elevation, fluoroscopic screening of diaphragmatic movements, or electrical stimulation of phrenic nerves.1-4 Our patient had a lymphocytic meningitis with sensory and motor neuropathies including bilateral phrenic nerve palsies. Diaphragmatic paralysis due to Lyme disease was diagnosed on the basis of clinical features, chest ultrasonography, the presence of the tick head, and serology indicating a recent infection with B. burgdorferi as well as a rapid response to antibiotic therapy.

The clinical diagnosis of Lyme disease may be supported by serologic testing. B. burgdorferi antibody tests may be negative in early infection, but patients are usually seropositive at or shortly after presenting with neurological symptoms. In some patients, antibodies against B. burgdorferi may be detectable in CSF slightly earlier than serum. Culture and B. burgdorferi deoxyribonucleic acid detection using polymerase chain reaction may also be used but were not in our case.

The three patients reported in the literature with respiratory failure caused by neuroborreliosis were ventilated for 3 months, 1 month, and 13 months, respectively, whilst our patient required ventilation for only 22 days.1-4 We speculate that early recognition of the possibility of Lyme disease and appropriate treatment shortened our patient’s acute illness.

In conclusion, it is important to consider Lyme disease in the differential diagnosis of acute respiratory failure – with or without erythema migrans.

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References


Benign paroxysmal positional vertigo (BPPV) predominantly affects the right labyrinth

We read with great interest the article ‘Benign paroxysmal positional vertigo predominantly affects the right labyrinth’, by M von Brecvern et al., which prompted us to review our data of the last 10 years (1995–2004).

A total of 661 patients, referred to the ear, nose, and throat department or to the neurology department, were diagnosed as having benign paroxysmal positional vertigo (BPPV) in its various forms. The pathology was located in the posterior canal in 477 patients, in the horizontal canal in 142, and in the anterior canal in 22. Multiple canals were affected in 20 patients (table 1).

The right ear was 1.50 times more frequently involved than the left. The predominance of the right ear was seen in all types of BPPV (table 1).

Hence, our data confirm the preponderance of right sided BPPV. The predilection of right sided BPPV was seen in all variants. Horizontal canal BPPV was observed in 22%, confirming our previous data.1 This number is higher than in other series.4 The apogeotropic form should not be considered as a rarity as it contributes to 23% of horizontal canal BPPV in our series and 38% in the series of Casani et al.1

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Table 1

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Horizontal canal</th>
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<tbody>
<tr>
<td></td>
<td>Posterior canal</td>
</tr>
<tr>
<td></td>
<td>Geotropic</td>
</tr>
<tr>
<td>Right n = 379</td>
<td>266</td>
</tr>
<tr>
<td>Left n = 253</td>
<td>185</td>
</tr>
<tr>
<td>Bilateral n = 29</td>
<td>26</td>
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<td>72%</td>
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Total n = 661
Aciclovir induced posterior leucoencephalopathy

Aciclovir is an extremely effective agent for the treatment of herpes simplex encephalitis and varicella–zoster infections in immunocompromised individuals.1 Encephalopathy induced by aciclovir is an infrequent but well recognised adverse effect of aciclovir.2 The predisposing factors to aciclovir induced encephalopathy (AIE) include age, acute or chronic renal failure, and other neurotoxic drugs. Tremors (40–58%), disorientation (40–90%), agitation (22–30%), hallucinations (25%), and delirium (23%) are common presentations of AIE, whereas seizures (10%), cerebellar ataxia (11%), sensory symptoms (9%), speech disorders (9%), fever (5%), and cranial nerve palsies (0%) are much less frequent.2 The supportive diagnostic criteria for AIE include a temporal association between the symptoms and aciclovir use, as well as acellular cerebrospinal fluid (CSF) in cases without herpes simplex or varicella–zoster encephalitis. In the majority of cases symptoms develop within 72 hours of starting aciclovir treatment, although up to 120 days has been reported.3 The clinical recovery may take several days (five days in 57% of cases) following discontinuation of aciclovir.4 The EEG typically shows diffuse slow wave activity rather than focal abnormalities.5

The radiological features are not well described in AIE. Case reports have identified multifocal white matter signal abnormalities involving the cerebellum, pons, and periventricular region as well as evidence of vascular encephalopathy on MRI.6 7 We report a case of AIE with MRI features consistent with posterior leucoencephalopathy with clinical and radiological improvement following the discontinuation of aciclovir, along with raised serum and CSF concentrations of aciclovir and 9-carboxymethoxymethylguanine (CMMG), the main metabolite of aciclovir.

Case report

A 47 year old woman with a 15 month history of cANCA5 glomerulonephritis and chronic end stage renal failure (serum creatinine 957 μmol/l), managed on continuous ambulatory peritoneal dialysis, azathioprine (100 mg/day), and prednisolone (10 mg/day), developed a mid-thoracic varicella–zoster rash. She was given a reduced dose of intravenous aciclovir (250 mg three times daily). Within 48 hours she became agitated, developed visual hallucinations and drowsiness (Glasgow coma scale (GCS): overall 6; eye 1, motor 4, verbal 1). On admission to the intensive care unit she was apyrexial, the highest blood pressure recorded was 180/104 mmHg while agitated, and fundoscopy was unremarkable. The tendon reflexes were exaggerated, with extensor plantar responses. Oculocephalic and corneal reflexes as well as spontaneous respiration were present.

Laboratory investigations showed a haemoglobin of 9.7 g/l, white cell count 5.8×10⁹/l, urea 22 mmol/l, ESR 90 mm/h, C reactive protein 27 mg/l, albumin 22 g/l, ammonia 10 mmol/l, and cANCA negative. Computed tomography of the head, done immediately after she became obtunded, showed posterior white matter hypodensities. The lumbar CSF contained no white cells and four red blood cells per mm³, with a protein of 0.63 g/l and a CSF/serum glucose ratio of 3.96:1. The opening pressure was 41 cm. CSF cultures, including culture for acid fast bacilli, were negative. CSF testing by polymerase chain reaction was negative for herpes simplex virus 1 and 2, varicella–zoster virus, cryptococcal antigen, and JC virus. An EEG showed excessive slow wave activity. Magnetic resonance imaging (MRI) of the brain and an MR venogram (done after five days on aciclovir) showed symmetrical posterior white matter changes predominantly in the occipital and parietal lobes (fig 1A and 1B) without evidence of venous sinus thrombosis, gadolinium enhancement, or matched defects in diffusion weighted images.

On admission, azathioprine was stopped and intravenous methylprednisolone (500 mg/day for three days) was started for presumed CNS vasculitis. There was no improvement 72 hours after this treatment and after eight days of aciclovir. Aciclovir was discontinued when AIE was suspected, and peritoneal dialysis was maintained. Within 48 hours of discontinuation of aciclovir, the GCS improved (eye score 3, motor score 6, verbal score 3) and neurological examination showed bilateral upper limb postural tremor, which resolved over 24 hours. The Addenbrooke’s score was 77/100. Repeat MRI (fig 1C, 1D) showed a significant improvement. Analysis of aciclovir and CMMG levels in the serum and CSF showed high values, at levels generally associated with neurotoxicity.7 The serum aciclovir and CMMG concentrations were, respectively, as follows:

- 5 days post-aciclovir initiation: 34.9 μmol/l and 91.7 μmol/l;
- 6 days post-aciclovir: 35.4 μmol/l and 148.5 μmol/l;
- 7 days post-aciclovir: 17.2 μmol/l and 141 μmol/l.

The CSF aciclovir and CMMG concentrations four days post-aciclovir initiation were, respectively, 5.99 μmol/l and 2.25 μmol/l (CMMG levels are not detectable in CSF unless there is neurotoxicity (Heßdäen A, submitted for publication)), supporting a diagnosis of AIE.8

Comment

The clinical presentation of our patient, her rapid recovery, and the CSF and EEG findings are characteristic of AIE associated with herpes simplex or varicella–zoster encephalitis.9 5 The lack of significantly raised blood pressure or papilloedema excludes hypertensive posterior leucoencephalopathy. ANCA vasculitis causing posterior leucoencephalopathy has been reported but only in the presence of severe hypertension. AIE, an infrequent but well recognised adverse effect of aciclovir, has until now been diagnosed

![Figure 1](image-url)
mainly on clinical features. Factors predisposing to AIE include age, acute or chronic renal failure, and other neurotoxic drugs. The diagnosis is facilitated by analysis of aciclovir and CMMG in serum and CSF. In cases with renal failure, the half life of aciclovir extends from 3 to 20 hours and as a result aciclovir is metabolised to CMMG by alcohol and acetyldyne dehydrogenases. At present, reliable dose recommendations are not available for patients with renal failure.

In a case study of 93 patients, mainly with renal failure, we found mean (SD) aciclovir concentrations of 21.0 (30.7) μmol/l (in 49 patients with neurotoxicity) and 7.2 (6.7) μmol/l in 44 asymptomatic patients receiving aciclovir), while CMMG concentrations were 34.1 (39.4) μmol/l in patients with neurotoxicity and 4.7 (4.7) μmol/l in asymptomatic patients. CMMG levels of >10 μmol/l seemed to be associated with neurotoxicity. A high CMMG level is a strong predictor of AIE in patients with renal failure. Haemodialysis is effective in clearing aciclovir and CMMG, and to a lesser extent so is peritoneal dialysis.

This case highlights the difficulties in diagnosing AIE and the value of measuring aciclovir and CMMG levels in making the diagnosis. In cases with renal failure and herpes simplex or varicella-zoster encephalitis, aciclovir should not be discontinued prematurely, but a total daily dose exceeding 400 mg is not generally recommended in patients with renal impairment.

Pharmacokinetic studies of aciclovir and CMMG are being undertaken at Karolinska University Hospital, Sweden, with the aim of achieving dose recommendations for patient with renal failure.

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References


Normal memory and no confabulation after extensive damage to the orbitofrontal cortex

Subarachnoid haemorrhage caused by the rupture of an anterior communicating artery (ACoA) aneurysm is often followed by amnesia, confabulation, and personality change including social decision making. However, the regions responsible for each symptom have not been determined conclusively. We describe a patient who showed personality change, but neither memory impairment nor confabulation, after extensive damage to the bilateral orbitofrontal cortex demonstrated by magnetic resonance imaging, providing evidence that the destruction of the medial orbitofrontal cortex alone cannot cause amnesia and confabulation.

Case report

The patient was a 45 year old, right handed man with a 16th grade education. He was not an apathetic person and worked hard as a manager before the onset of his illness (in terms of lack of concern for others including his family, his appearance, and his future; the loss of spontaneity, disinhibition, impaired decision making, and rigidity of thought) generally agreed in the literature to be the result of dysfunction of the frontal lobe, particularly the orbitofrontal cortex. Importantly, the patient showed no memory deficit. Damage to the basal forebrain without damage to the frontal lobe causes amnesia. With regard to the orbitofrontal cortex, it has been argued that destruction of this region is not necessary for the development of amnesia or basic cognitive function. However, there has so far been no conclusive evidence as to whether or not damage to the orbitofrontal cortex alone results in amnesia and therefore strengthens the notion that the basal forebrain is one of the crucial sites for human memory.

It should be noted that the assessment of memory in our present study is based on standardised tests. This means that memory that is not measurable using these standardised tests (for example, temporal context memory) may be related to the function of the orbitofrontal cortex. We cannot draw a strong conclusion regarding frontal lobe function, because we did not use tests sensitive to damage to the ventromedial prefrontal cortex (for example, the Iowa Gambling Task).

The patient showed no confabulation. Damage to the orbitofrontal lobe alone might not be sufficient for confabulation to be
manifest. In one study, confabulation was seen in amnesic but not in non-amnesic patients with rupture of the ACoA and frontal lobe lesions, and in another study of amnesic patients with rupture of the ACoA, only those with frontal lobe lesions showed confabulation, suggesting that both frontal lobe lesions and amnesia are necessary for the development of confabulation. In contrast, a patient with confabulation and amnesia after damage to the basal forebrain but without frontal lobe damage has been reported. Further studies involving comprehensive neuropsychological and magnetic resonance imaging examination are needed to determine whether both frontal and basal forebrain involvement or basal forebrain involvement alone is required for the manifestation of confabulation.

Figure 1 (A) Sagittal and (B) coronal T2 weighted magnetic resonance images showing extensive lesions in the bilateral orbitofrontal cortex. The core structures of the basal forebrain (medial septal nucleus, vertical and horizontal limb nuclei of Broca’s diagonal band, and nucleus basalis of Meynert) were not damaged. In the sagittal sections, the images in the upper row show the right hemisphere and those in the lower row show the left hemisphere. In each row, the first, second, and third images are 15 mm, 10 mm, and 5 mm away from the longitudinal cerebral fissure, respectively. In the coronal sections, the left side of the image corresponds to the right side of the brain. In the upper row, the first, second, and third images are 0 mm, 5 mm, and 10 mm rostral from the anterior commissure. In the lower row, the first, second, and third images are 20 mm, 30 mm, and 50 mm rostral from the anterior commissure.

Adult onset SSPE: experiences in West Yorkshire over a 12 month period
Subacute sclerosing panencephalitis (SSPE) is a rare delayed complication of measles virus infection in infancy. It is characterised by behavioural changes, myoclonus, cognitive impairment, visual disturbance, pyramidal and extrapyramidal signs, and ultimately coma leading to death. Typically, SSPE presents in childhood or early adolescence, but adult onset cases are recognised. Widespread measles immunisation in the UK has led to a dramatic fall in the incidence of SSPE in children, leading to the disease almost becoming extinct. However, a latent disease pool remains and cases may still come to the attention of adult neurologists, as borne out by our recent experience in West Yorkshire.

Case histories
An 18 year old man gave a three week history of blinking episodes lasting approximately one second, associated with a brief head jerk. These were not present in sleep. Examination revealed myoclonic jerks involving the neck associated with blinking. Initial electroencephalograms (EEGs), blood tests, and a magnetic resonance imaging scan were normal. Several anticonvulsant medications failed to suppress the jerks, which by four weeks had spread to the legs, causing unsteadiness. The mini mental test examination score at this stage was 26 of 30. He began to deteriorate rapidly, with disorientation, blurred affect, dystonic posturing of the left arm, bradykinesia, and rigidity. Cerebrospinal fluid (CSF) was sent for analysis of 14-3-3 and S-100 proteins, which were negative. A further EEG, nine weeks after onset, demonstrated high voltage periodic complexes occurring every 10 seconds, consistent with SSPE. CSF and serum measles titres were raised at 35110 mIU/ml and 152930 mIU/ml respectively. The CSF to serum albumin ratio was 1:300, consistent with intrathecal antibody synthesis. There was no past history of measles, although he had received MMR (measles mumps rubella) immunisation at age 9. Oral inosiplex (isoprinosine) and subcutaneous interferon 92b were started and an Ommaya reservoir was inserted to administer intraventricular interferon 92b. By this stage, the myoclonus had subsided but he had gaze paresis, mutism, widespread spasticity, and required gastrostomy feeding. He received intraventricular treatment for six weeks before reservoir infection necessitated its removal. His condition plateaued and he was maintained on inosiplex alone. Eventually, he was discharged home in a dependent state.

References

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A 25 year old woman presented to her general practitioner complaining of impaired concentration, mood swings, disturbed sleep, and memory loss. One month later, she had noticed a fine tremor in both hands and occasional spasms affecting her right foot. Her concentration was worse and she mentioned word finding difficulties. She also had a tremor in her fingers and had fallen. She was seen by a psychiatrist and somatisation was initially suspected. Later, she was referred to a neurologist. He noted that she had been acting oddly—for example, being found by her mother in a bath of cold water. Neurological examination was normal except for a mini mental test examination score of 20 of 30 with a child-like effect and stilted speech. A magnetic resonance imaging scan was unremarkable. She continued to deteriorate, developing right sided myoclonus. By this stage, she was unable to perform simple tasks, such as washing, and was aware of crawling sensations all over her body. Six months after her first presentation she had an EEG. This revealed repetitive complexes occurring every four to six seconds, often associated with a myoclonic jerk and consistent with SSPE. CSF analysis confirmed oligoclonal bands not present in the serum, which were positive for measles antibody antigen by immunoblotting. She had contracted measles at age 11 months. She was started on oral piracetam and inosiplex, along with subcutaneous interferon $\alpha$-$b$, but she became bed bound with quadriparesis, dysarthria, and diffuse hyperalgesia. Her treatment was changed to intraventricular interferon $\alpha$-$a$ administered via an Ommaya reservoir. She required continuous infusions of midazolam and diamorphine for symptom control, and nasogastric feeding was started. Her condition subsequently stabilised and she was discharged to a children’s hospice.

Discussion

The estimated incidence of SSPE each year in developed nations is <1/100 million of the population under the age of 20. The occurrence of two adult cases in the small region of West Yorkshire (population two million) within a few months of one another is remarkable. Although probably a chance finding, our experience emphasises the need for continued surveillance in populations where measles is no longer endemic. In theory more adult onset SSPE cases could present to neurologists in the future. This is because slow central nervous system spread of the virus over many years leaves open the potential for SSPE to present in later life, decades after population eradication of measles. In addition, routine immunisation has led to a shift in the incidence of measles towards unprotected children age <1, who are at a higher relative risk of developing SSPE in later life after a longer incubation period. Recently, there has been an increase in the number of measles outbreaks after a decline in the uptake of the combined MMR immunisation because of safety fears.1

In our patients, SSPE was not initially suspected as a diagnosis in the first instance. Enquiring about measles in childhood may have been helpful in case 2, but not case 1, because infection in infancy was probably subclinical. In this patient the lack of typical findings on initial EEG led to further delay, and instead we considered variant Creutzfeld Jakob disease as a possibility. Patient 2 presented with early cognitive and behavioural changes. Initially, patients may come to the attention of other specialties with non-specific or psychiatric symptoms.2 It was only subsequent worsening of the patient’s mental state associated with the development of unilateral myoclonic jerks that prompted further investigation, including EEG.

There is no curative treatment for SSPE. Trials have been complicated by variable natural history and spontaneous long remissions of the disease, although it is eventually fatal (median survival, three years). One study demonstrated similar response rates among patients randomised to inosiplex, with or without intraventricular interferon $\alpha$-$b$ treatment for six months (35% v 34%).3 However, these figures were substantially higher than historical remission rates of between 5% and 10%. In our hands, intraventricular interferon was associated with initial worsening of encephalopathy and pronounced hyperpyrexia, possibly the result of chemically induced meningitis, and serum interferon infection was a further complication. In both patients, disease appeared eventually to stabilise after antiviral treatment, particularly in patient 1, in whom rapid progression at onset was suggestive of fullblown SSPE, usually fatal within three months.

Prevention seems to be the best approach, with mass immunisation leading to a drastic reduction in reported cases of measles and associated complications. However, our experience suggests that this failure should not be forgotten. Clinicians should remain vigilant for this devastating disease.

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References


L laterality of symptoms in patients admitted to a stroke unit who had a diagnosis of a psychiatric condition

Some psychiatric conditions produce symptoms that can mimic an acute neurological disease, including stroke.2,3 In several studies, such symptoms seemed to be more common on the left side of the body.4,5 The predominant processing of emotional information by the right hemisphere offers a hypothetical explanation for this finding.

We reviewed the discharge summaries of patients who were admitted to a stroke unit during the period May 1996 to December 2003 with a diagnosis of acute stroke and who had a discharge diagnosis of somatoform disorder and/or anxiety disorder according to the DSM-IV, revised criteria, and no recent stroke, according to the World Health Organisation definition.6

Two investigators (CS and LC) reviewed the discharge summaries independently and collected the following data in a standardised form: (a) age; (b) sex; (c) discharge psychiatric diagnosis (somatoform disorder and conversion disorder; anxiety disorders: generalised anxiety disorder and panic disorder); (d) type (motor paresis and/or involuntary movements, sensory, visual, other) and side (right, left, bilateral) of the symptoms; (e) vascular risk factors; (f) neuroimaging data; and (g) length of stay. Disagreements were solved by consensus.

RESULTS

From 2279 consecutively admitted patients to our stroke unit, we included 35 (1.5%) discharge summaries for review. Of these, 25 patients had received a diagnosis of somatoform disorder and/or anxiety disorder and 11 with conversion disorder), and 7 patients had a diagnosis of anxiety disorder (4 with generalised anxiety disorder and 3 with panic disorder). Three patients had other psychiatric diagnoses. Symptoms were presented on the left side of the body in 11 patients, on the right side of the body in 14, and on bilateral presentation (table 1). There were 21 patients (60%) with vascular risk factors, of whom 11 (31.4%) had more than one risk factor. Median hospitalisation stay was 3 days. There were no statistical differences in demographic variables, discharge psychiatric diagnosis, type of the symptoms, vascular risk factors, neuroimaging data, or length of stay between patients with left sided symptoms and those with right sided symptoms concerning (table 1). Patients with somatoform disorders had more motor symptoms most frequently than did patients with anxiety disorders ($\chi^2 = 6.84; p = 0.02$).

DISCUSSION

In this study, 1.5% of the patients admitted to a stroke unit presented symptoms unexplained by stroke or other neurological disease and fulfilling the criteria for psychiatric diagnosis. Contrary to most published studies, our results did not show a preponderance of left sided symptoms. In a meta-analysis of all studies describing patients with medically unexplained symptoms, Stone et al concluded that it is not certain that the functional symptoms are more common on the left side than on the right side of the body. They found a preponderance of the left symptoms only in the studies in which investigators were aware of the laterality hypothesis before performing the study. As in that meta-analysis, we did not find a preponderance of left sided symptoms.

The younger median age and female preponderance of patients with psychiatric conditions mimicking a stroke reflects the demographic characteristics of somatoform.
and anxiety disorders. One interesting finding was the high frequency of vascular risk factors, which increases diagnostic uncertainty and could explain the admission to the stroke unit. A major limitation of our study is the lack of use diffusion magnetic resonance imaging to exclude definitively the unlikely possibility of a concomitant ischaemic lesion.

We conclude that left sided laterality of symptoms cannot be used as a tool to establish a psychiatric diagnosis in patients with acute lateralised neurological symptoms.

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BOOK REVIEW

Atlas of neuromuscular diseases

This book it titled an “atlas” and subtitled “a practical guideline”. I had the expectation of a heavily illustrated book of neuromuscular conditions with annotations. The book has been designed as a comprehensive coverage of disorders of peripheral nerve (including cranial nerves), muscle, neuromuscular junction, and motor neuron. Each condition is outlined in note form, with particular emphasis on causation—which can be lengthy and repetitive. The style of the text is abbreviated and can be difficult to read. The précis can be misleading or inaccurate at times. A useful list of references is given.

It is not clear to me to whom this book would appeal. The text is probably too comprehensive and potentially misleading or confusing for students, and does not add much to those already informed. The number and quality of the illustrations is disappointing. I had expected more clinical illustrations of the conditions described. As a practical guideline it is not helpful and in particular the therapeutic suggestions are too abbreviated, incomplete, and uncritical for clinical application. Problems to be addressed in the next edition include the use of the same nerve biopsy illustration for patients with chronic inflammatory demyelinating polyneuropathy and Charcot-Marie-Tooth disease, despite one image being rotated by 90 degrees; the illustration of text relating to genetically defined young onset spinal muscular atrophy with an elderly man who appears to have progressive muscular atrophy; and the spelling of fascioscapulohumeral (sic) dystrophy.

The authors point out that “no other book provides a complete overview in a structured and easily comprehensive pattern supported by figures and pictures”. There are, however, a number of excellent books related to diseases of muscle and nerve, some providing a wider range of clinical and pathological illustrations and a more critical review of clinical presentation, diagnosis, and treatment. At the present time the role claimed by this book remains unfilled.

R W Orrell