

Case report

Central deafness in a young child with Moyamoya disease: Paternal linkage in a Caucasian family Two case reports and a review of the literature

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Abstract

A case of 'central deafness' is presented in a 3-year-old male Caucasian child with Moyamoya disease (MMD); a rare, progressive and occlusive cerebrovascular disorder predominantly affecting the carotid artery system. Documentation of normal peripheral auditory function and brainstem pathway integrity is provided by acoustic admittance, otoacoustic emission and brainstem auditory evoked potential measurements. The lack of behavioral response to sound, and absent middle and long latency auditory evoked potentials suggest thalamo-cortical dysfunction. Magnetic resonance imaging showed diffuse ischemic damage in subcortical white matter including areas of the temporal lobes. In addition, there were multiple and focal cortical infarctions in both cerebral hemispheres, focused primarily in the frontal, parietal and temporal areas. Taken together, these structural and functional abnormalities in addition to severely delayed speech and language development are consistent with the diagnosis of central deafness and suggest a disconnection between higher brainstem and cortical auditory areas. The child's father also has MMD, but was diagnosed only recently. The presence of paternal linkage is informative since it rules out x-linked recessive and maternal inheritance. To our knowledge, this represents the first documented case of paternal linkage in MMD with central deafness in a Caucasian child with no apparent Japanese ancestry. Herein, we focus on central auditory dysfunction and consider how lesion-induced changes have contributed to a deficit in basic auditory responsiveness, including a severe disturbance in receptive and expressive auditory-based speech and language skills. © 1999 Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

Moyamoya disease (MMD), or the spontaneous occlusion of the circle of Willis, is a bilateral, progressive and occlusive cerebrovascular disorder that is predominantly seen in childhood. It is characterized by narrowing or stenosis at the distal internal carotid arteries, and proximal portions of the anterior and middle cerebral arteries, secondary to intimal thickening [1,2]. Moyamoya disease can occur as a primary disease or as a syndrome in association with a large variety of conditions, including: Fanconi's anemia, Type I glycogenesis, congenital heart disease, neurofibromatosis, radiation vasculitis, renovascular hypertension, renal artery stenosis, persistent primitive trigeminal artery variant, Ito's hypomelanosis, Hageman factor deficiency, Down syndrome and Noonan syndrome [3–19].

The etiology and possible inheritance of MMD is thought to be multifactorial. This view is supported by the relatively high incidence found in Japanese and in certain affected families, the low incidence found in Caucasians and other racial groups [8,19–32] and the fact that acquired factors may also play a role [33]. Genetic and basic science studies are gaining new insight into the nature of this disease and these advancements will ultimately provide the basis for early identification and future treatments [1,33–53].

Based on the Japanese literature, MMD occurs more frequently in females than males (~ 1.7:1) and there are two chronological peaks in incidence [1,2]. A prominent peak occurs in the first decade of life, usually around 4 years of age, and another much smaller peak, occurs in the fourth decade of life [1,54]. The course of the disease is different in these two groups. In children, transient ischemic attacks (TIAs), multiple cerebral infarctions, hemiplegia, seizures, headache and developmental delay are frequently observed. These dysfunctions can be manifest in intellectual deficits, disturbances of consciousness, visual problems, motor dysfunction, and speech disorders of an aphasic nature.

Whereas hemorrhagic presentation is rare in children, serial angiographic studies show that this disease is progressive [54] and can be classified into six stages [18]. In the initial stage, angiographic features show stenosis at the distal portion of the internal carotid artery with prominent collateral and perforating vessels at the base-of-the-brain. The characteristic appearance of these vessels on angiography gives rise to the term 'Moya Moya', a Japanese adjective for 'something hazy like a floating puff of cigarette smoke' [55]. In the intermediate stages as ischemia increases, these vessels proliferate and in the final stages, the Moyamoya vessels involute. These pathophysiologic changes result in the brain being perfused by only collateral branches of the external carotid, ophthalmic, and vertebrobasilar artery systems [56]. Once the occlusive process has arrested and collateralization has maximized, the clinical course typically stabilizes [57].

Medical treatments with steroids and vasodilators and surgical sympathectomies have not resulted in long-term improvements [54]. In contrast, excellent long-term results have been achieved through revascularization procedures such as the encephalo-duro-arterio-synangiosis (EDAS) [58]. These operations have become the treatment option of choice, which is advocated in all children prior to the onset of permanent neurological deficits. Surgical intervention can also minimize further neurological deterioration by preventing additional TIAs and strokes and in some instances even reversing apparently fixed deficits [54,57].

Whereas the literature on MMD has been concerned predominantly with identification, treatment, basic science and genetic issues, functional outcomes, except for isolated case studies, have not been well described until recently [59–63]. Herein, we document a case of central deafness in a 3-year-old male Caucasian child with MMD who underwent successful EDAS. We provide additional evidence that the child's father has MMD, but was diagnosed only recently.

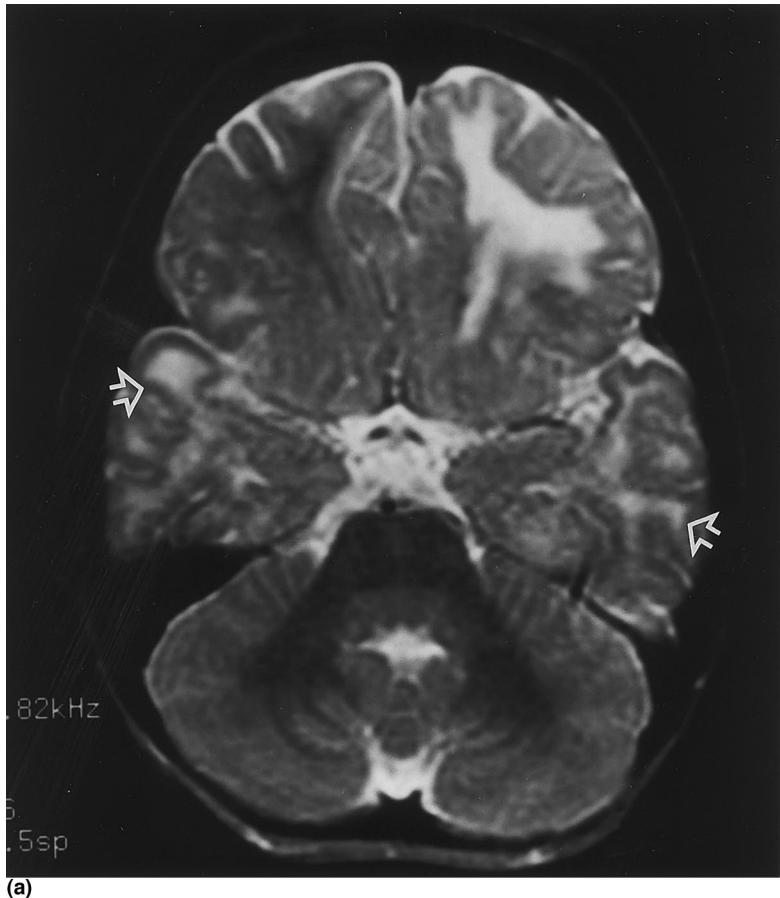


Fig. 1. Axial (a and b) and coronal (c) spin-echo T2-weighted (TR 3000 ms, TE 85 ms) MRI scans of case 1 demonstrate multiple areas of cortical and subcortical infarction, most extensive in the left frontal lobe. There is diffuse ischemic change noted in subcortical and cortical areas including the temporal lobes (open arrows in a and c). The stenosis at the left ICA terminus is demonstrated (arrow in c). The cerebellum and brainstem are normal. The MRI assessments were performed on a clinical 1.5 T GE-SIGNA scanner (GE Medical Systems, Milwaukee, WI).

2. Case reports

2.1. Case 1

A 15-month-old male Caucasian child, who was previously healthy, with appropriate developmental milestones, presented to the hospital with partial seizures, head deviation to the right and mental-status changes. The seizures were controlled and the patient was maintained on anti-seizure medications. Computed tomography (CT) of the head showed diffuse white matter disease with a predominance in the left frontal lobe.

Magnetic resonance imaging (MRI) revealed similar findings (Fig. 1a–c). The presumed working diagnosis was leukodystrophy and the appropriate laboratory tests were obtained.

One week later, he developed acute left hemiparesis and returned for re-evaluation. There had been no intercurrent seizures and he tolerated phenobarbital well. Magnetic resonance imaging was repeated and revealed persistence of the white matter disease, with a new large right frontal infarct and bilateral parietal-occipital infarcts, with the one on the left being more acute than the one on the right. Electroencephalography (EEG)

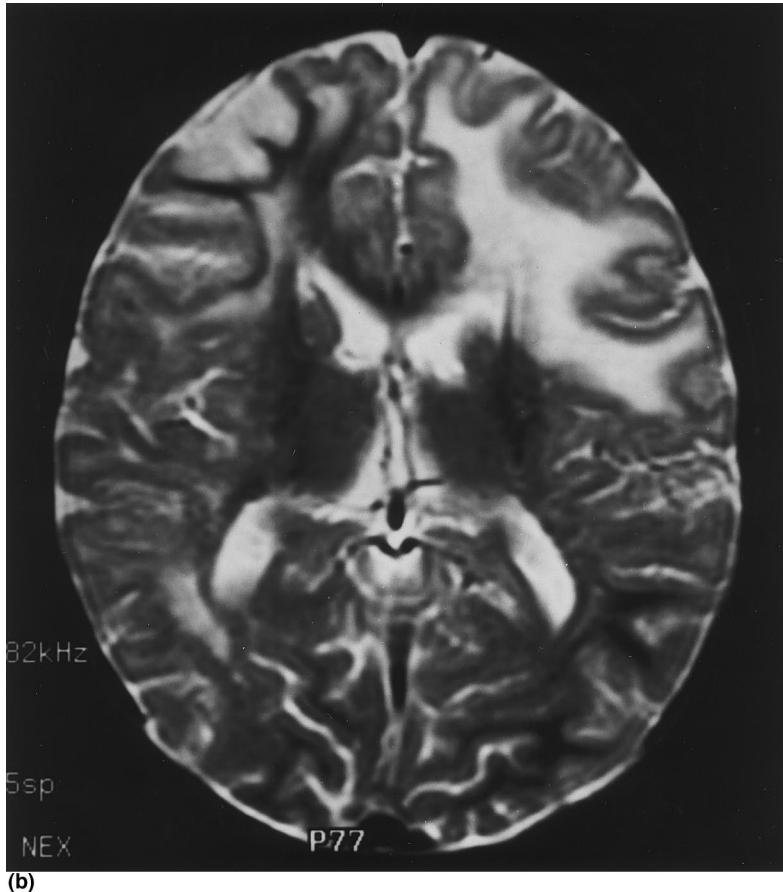


Fig. 1. (Continued)

revealed diffuse slowing in the 2–4 Hz range with absent beta activity over the right hemisphere. There were no epileptiform patterns. Evaluation for hypercoagulable states and vasculitis were unrevealing. Echocardiogram was normal. Cerebral angiography (Fig. 2a–c) confirmed the diagnosis of MMD. Two weeks later, he underwent bilateral EDAS as a staged procedure. In the month following surgery, he experienced several further strokes and frequent bouts of migraine-like episodes with pallor, vomiting and discomfort (presumed head pain by the parents). These problems resolved over a 3–4 month period. A repeat cerebral angiogram 1 year after the EDAS procedures showed neovascularization from the pial anastomoses. Importantly, and to date, he has had no further strokes. Because of concern that

he was not progressing in the area of speech and language development, behavioral audiological testing and subsequent electrophysiologic studies were performed.

2.2. Case 2

A 28-year-old white male is the biological father of the young child described above. Family history was notable for the father having developed normally until 3 years of age when he experienced a seizure. The medical work-up was unrevealing at that time. One year later, he experienced an episode of transient lethargy, blindness and left-body weakness. The blindness and body weakness resolved over the course of 1 week. Phenobarbitol was started at that time and was

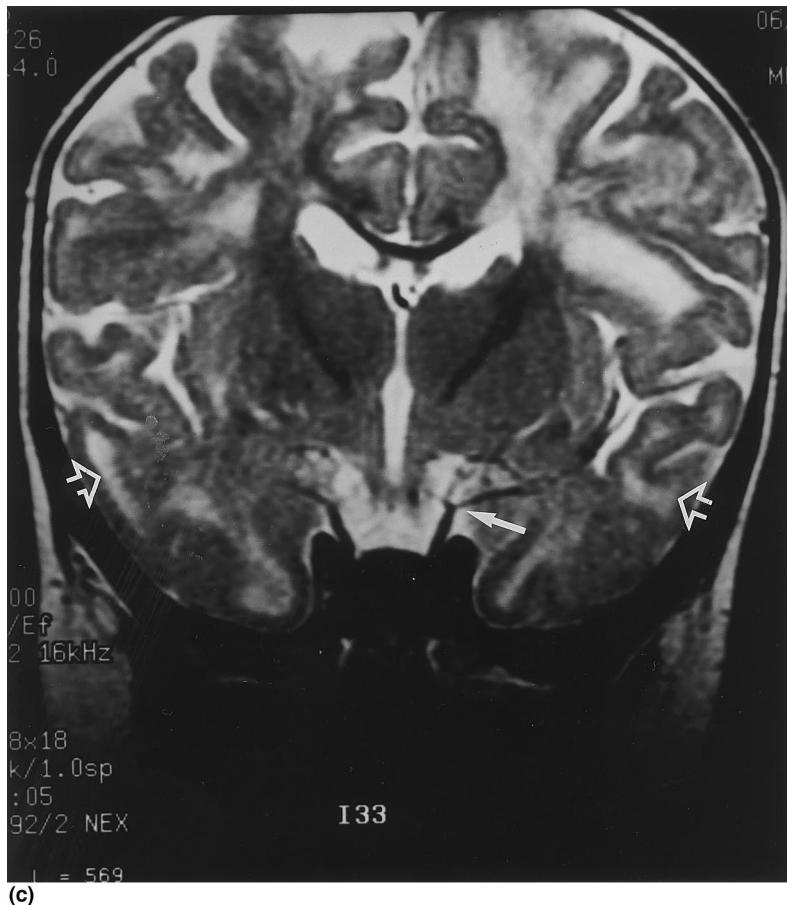
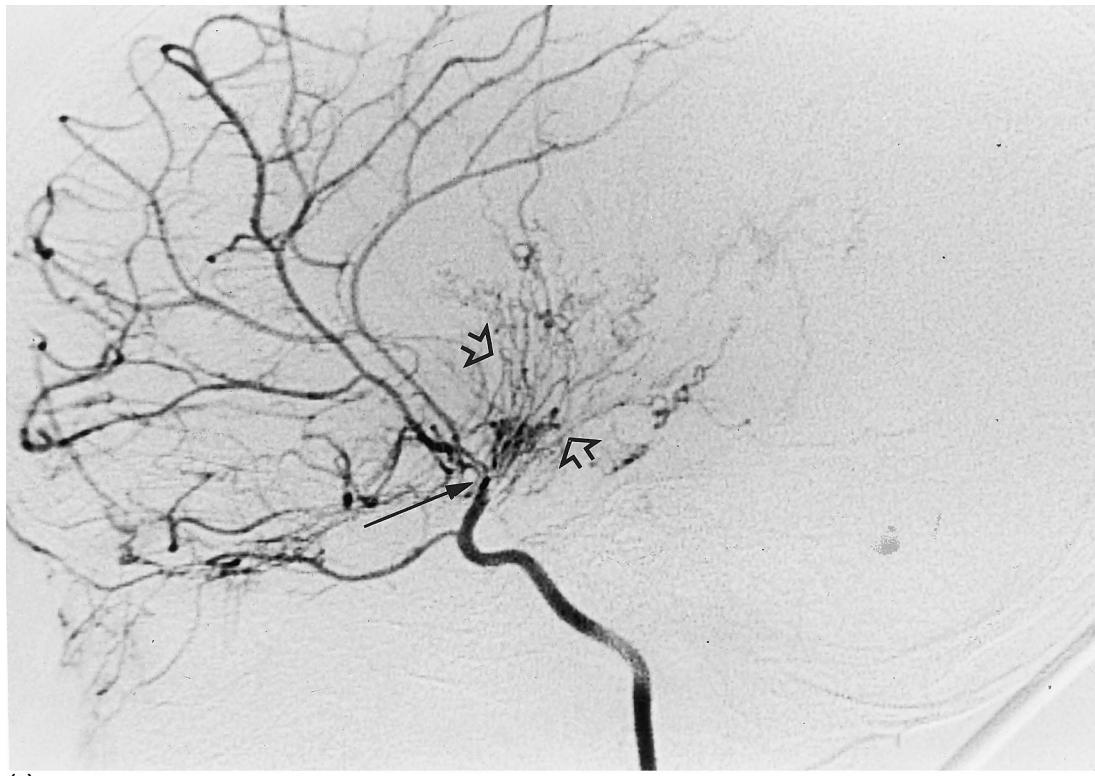


Fig. 1. (Continued)

discontinued in his teen years because of the absence of seizures and no deterioration in his neurological status. He was characterized as learning disabled but completed high school with a special diploma. However, he has been unable to secure employment. An episode of vomiting, fever and weakness occurred at 23 years of age. A diagnosis of viral meningitis was made and he recovered without any new neurological difficulties. His current difficulties include poor hand–eye coordination, decreased ability to read (5th grade level) and to perform mathematics (3rd grade level).

He was recently evaluated at our institution at

28 years of age, during the same general time period in which auditory studies were performed on the child. Neurological exam demonstrated saccadic pursuit movements, reduced grip in the left hand, decreased pin prick in the left hand and forearm, and dysdiadochokinesia in both hands. The left arm was kept semiflexed during ambulating and reflexes were more brisk on the left, with a left Babinski sign. Recent MRI (Fig. 3) and magnetic resonance angiography (MRA) (Fig. 4) revealed bilateral chronic infarctions and bilateral supraclinoid occlusion of the internal carotid arteries with increased blood flow in the middle meningeal arteries.



(a)

Fig. 2. Digital subtraction angiography of case 1 showing lateral views of the right (a) and left (b) internal carotid artery injections, as well as the frontal view following left vertebral artery injection (c). Note the bilateral ICA terminus stenoses, (long arrows in a and b), absence of the right middle cerebral artery, occlusion of most of the left middle cerebral artery except for a prominent angular/parietal branch (arrowheads in b), and the Moyamoya vessels (open arrows), more prominent on the left.

3. Investigations and results

3.1. Case 1

3.1.1. Neuroradiology

Magnetic resonance imaging demonstrated multiple cortical infarctions in both cerebral hemispheres, primarily focused in the frontal, parietal and temporal lobes. There was also evidence for diffuse ischemic change in the subcortical white matter and in the temporal lobes (Fig. 1a–c). Cerebral angiography (Fig. 2a–c) demonstrated severe stenoses at the terminations of the internal carotid arteries, stenoses in the proximal anterior cerebral arteries and left middle cerebral artery and occlusion of the right middle cerebral artery. The Moyamoya vessels and enlarged lenticulostriate collateral arteries, were particularly prominent on the left side. Angiographically, the normal large vessels of the posterior circulation and the enlarged thalamo-perforating collateral arteries correspond to Stage 3 disease [18].

3.1.2. Auditory studies

3.1.2.1. *Behavioral audiology.* Testing was performed in a sound-field environment by two experienced pediatric audiologists (LMA, JAK). Using standard conditioning techniques and by observation, sound-field testing failed to elicit any consistent localization responses in the horizontal plane to either frequency modulated pure tones (0.25, 0.5, 1, 2, 4 kHz, levels ≥ 80 dB HL) or to live voice speech (85 dB HL). Acoustic-admittance testing at 226 Hz (peak admittance 0.4 mmho, left ear; 0.3 mmho, right ear, at normal peak pres-



Fig. 2. (Continued)

sures) was consistent with normal middle ear integrity. Taken together, the abnormal response behaviors to sound field auditory testing and the lack of speech and language development raised the concern that this child was severely hearing impaired or deaf. These observations prompted further electroacoustic (otoacoustic emission) and electrophysiologic (evoked potential) assessments.

3.1.2.2. Electroacoustic and electrophysiologic measures. These measurements were performed on two separate test sessions. In the initial session, transient (click) evoked otoacoustic emissions (TEOAEs) and brainstem auditory evoked potentials (BAEPs) were recorded. The OAEs were used to assess preneural, biomechanical aspects of cochlear integrity and the BAEPs were used to assess auditory sensitivity and brainstem integrity. On the second session, distortion product otoacoustic emissions (DPOAEs) and middle and long

latency auditory evoked potentials (MLAEPS; LLAEPS) were recorded. The middle and long latency AEPs were used to assess higher order aspects of CNS function. Because of the child's age, the evoked potential and otoacoustic emission recordings were made under light chloral hydrate sedation. In both instances, testing was uneventful and the reliability was considered good.

3.1.2.3. TEOAE assessment. Transient evoked OAEs were obtained using commercially available instrumentation (Otdynamics, ILO92) and the nonlinear testing protocol in the QuickScreen mode [64]. In this child, TEOAEs were present and robust over a bandwidth of 1.0–4.0 kHz bilaterally. Fig. 5 (top) shows an example of the TEOAE waveforms and associated power spectrum for one ear; the numeric quantification for both ears is provided in the table (Fig. 5, bottom).



Fig. 2. (Continued)

The presence of TEOAEs over this bandwidth is highly correlated with hearing sensitivity ≤ 25 dB HL.

3.1.2.4. Distortion product otoacoustic emission (DPOAE) assessment. Distortion product growth functions (i.e. $2f_1-f_2$ response magnitude versus stimulus SPL) were obtained to selectively sample different frequency regions of the inner ear to further confirm physiologic integrity of the auditory sensory receptor mechanism and to correlate these results with the TEOAE and BAEP measures. Six pairs of pure tone primary frequencies (f_1 and f_2) spanning an f_2 frequency range from 1001 to 6006 Hz were used, where: the f_2/f_1 ratio = 1.2, f_1 was + 10 dB greater than f_2 , and f_2 stimulus level changed from 60 to 35 dB SPL in 3-dB steps. Offset versus equal-level primaries further sensitizes the procedure for detecting cochlear hearing loss [65,66]. Normal DPOAE growth

functions, consistent with an intact cochlear amplifier, were obtained bilaterally at the various frequencies sampled (Fig. 6).

3.1.2.5. Brainstem auditory evoked potential (BAEP) assessment. Single channel BAEPs were obtained using a standard protocol and commercial instrumentation. One 1-cm gold-cup electrode was affixed to the scalp at the vertex (Cz), ipsilateral earlobes (A1 and A2) and at the forehead (Fpz). Interelectrode impedance was less than 5 k Ω . The EEG activity was differentially amplified between vertex and ipsilateral earlobe electrodes with the forehead serving as ground. Data were filtered between 150 and 3000 Hz and signal averaged over a 20.48 ms recording epoch. Stimuli were 100 μ s rarefaction polarity electrical pulses transduced through Etymotic ER3A insert earphones at levels ranging from 80 to 10 dB nHL and at a rate of 21.3/s. Brainstem AEPs were

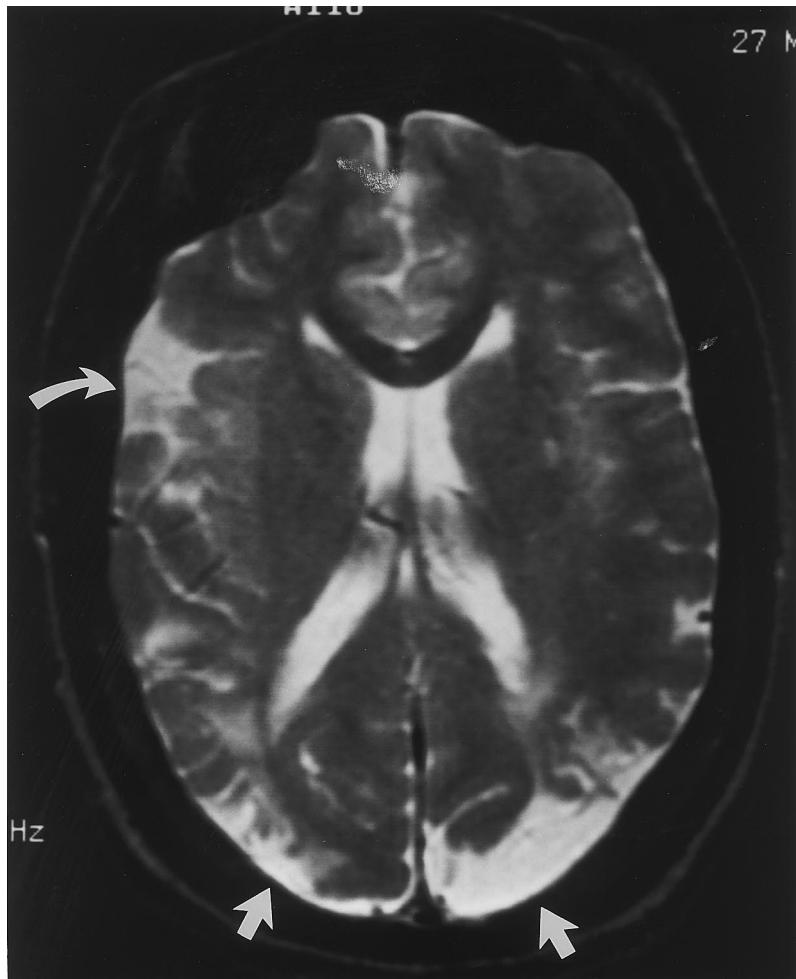


Fig. 3. Axial spin-echo T2-weighted (TR 2500 ms, TE 85 ms) MRI of case 2, which demonstrates focal cortical loss from previous infarctions in the occipital lobes (arrows) and in the right opercula area (curved arrow).

present, well developed and easily reproducible bilaterally (Fig. 7). Interpeak latencies were consistent with age level and click thresholds were less than 10 dB nHL bilaterally.

Middle and long latency auditory evoked potentials were recorded from 11 scalp electrodes (Cz, Pz, Fz, C3, C4, T3, T4, T5, T6, M1 and M2, all referenced to a balanced non-cephalic electrode. Electrode impedance was maintained less than 5 k Ω .

3.1.2.6. Middle latency auditory evoked potentials (MLAEPS). The recording epoch was from 0–70

ms. Stimuli were binaurally presented 1000-Hz tone bursts, (10 ms duration, 5 ms rise/fall times, shaped with a Blackman function, 5/s presentation rate, and at a level approximating 80 dB nHL). Binaural stimulus presentation was necessary because of time constraints. The EEG was digitized at 1000 Hz, amplified $\times 10000$ and filtered between 3.0 and 1000 Hz (Grass, Neurodata Acquisition System, Quincy, MA; SCAN and STIM systems, Neuroscan). Two separate runs of 2048 artifact free responses were recorded. Previous topographic studies indicate that MLAEPs have a predominant fronto-central fo-

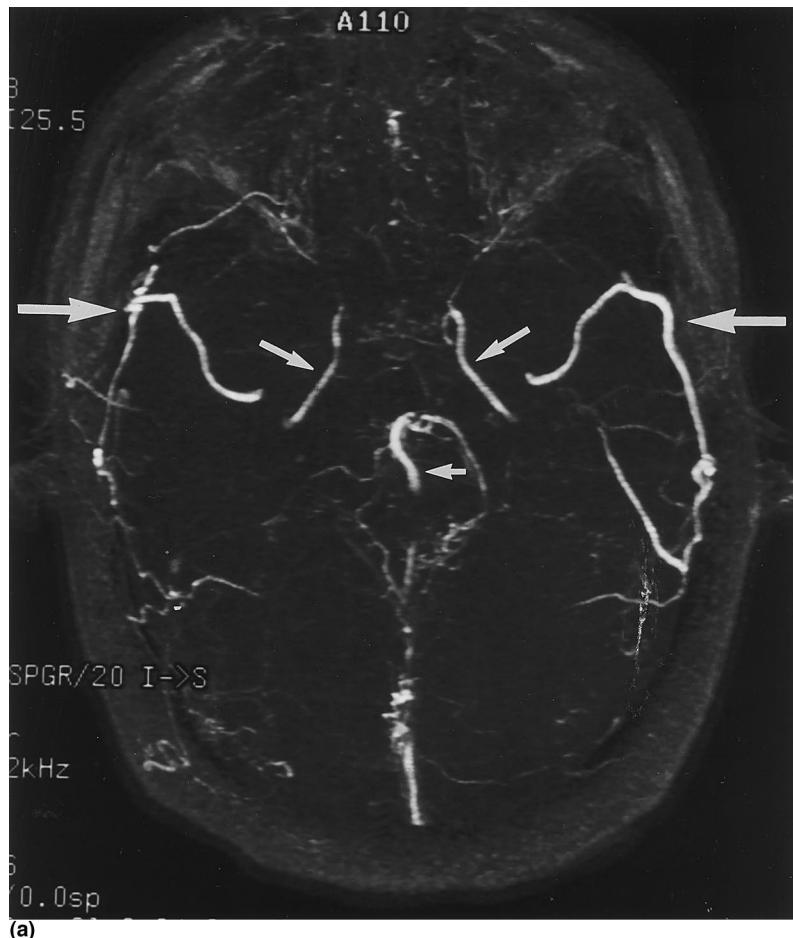


Fig. 4. Axial (a) and coronal (b) maximum intensity projections of 3D time-of-flight MRA of case 2 demonstrating small internal carotid arteries (arrows) without visible cerebral branches, a normal basilar artery (short arrows), and enlarged middle meningeal arteries (large arrows).

cus with additional components detectable over the lateral surface of the temporal lobe [67,68]. However, based on these recordings, no reliable time-locked activity to tonal stimuli in the middle latency range was detected at any of the scalp locations (Fig. 8, top) and only early latency BAEP components were clearly delineated.

3.1.2.7. Long latency auditory evoked potentials (LLAEPs). Because we were interested in knowing whether this child could process and discriminate auditory stimuli, we used a paradigm to study the mismatch negativity (MMN). The MMN is thought to be a preconscious, automatic response

of the brain to stimulus deviance that can be elicited in young children [69]. The standard stimuli were binaurally presented 1000 Hz tone bursts, 100 ms in duration presented at 80 dB nHL and at a probability of occurrence of 80%. Deviant (target) stimuli were 1500 Hz tone bursts, also 100 ms in duration, 80 dB nHL, but at a 20% probability level of occurrence. The recording epoch was 0–650 ms, including a 50 ms prestimulus interval. A total of 220 artifact free epochs were recorded. Data were recorded direct to disk on a trial-by-trial basis and were subsequently sorted, signal averaged, and baseline corrected off line. Two separate recordings were made. The MMN is

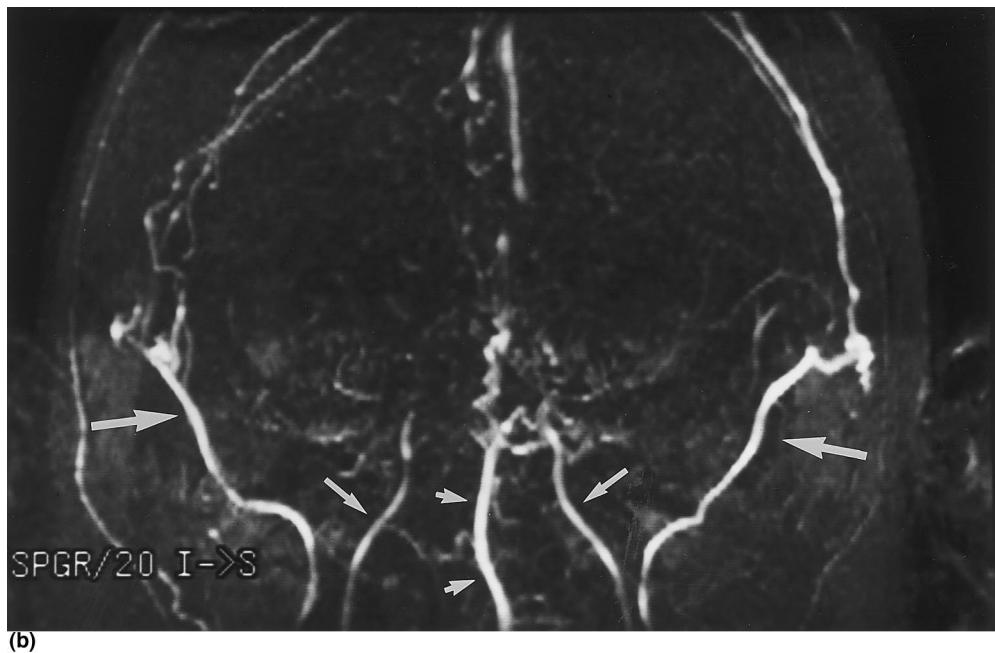


Fig. 4. (Continued)

typically obtained by subtracting the averaged standard from the averaged target (deviant) evoked potential waveform. In this case, because we were unable to elicit any consistent time-locked LLAEPs to either the standard or target conditions, the standard linear subtraction operation for evaluating MMN was non-contributory. Therefore, in Fig. 8 (bottom), we present two replications of LLAEP waveforms to standard stimuli, only to show the lack of waveform reproducibility to acoustic stimulation.

3.1.2.8. Speech and language measures. At the time of the auditory evaluations, speech and language development approximated that of a 2–4 month old infant. Expressive and receptive language was not age-appropriate and a general reduction in verbal expression began shortly after the initial presentation. Vocabulary was limited to simple two-syllable utterances /baba/ and /dada/ without sentence development. Comprehensive evaluation of the speech mechanism, articulation and psycholinguistic skills could not be determined due to the child's distractibility and developmental delay.

3.1.2.9. Neuro-ophthalmologic examination. Visual fields, visual acuity and confrontation could not be evaluated. However, the child was able to track small and medium sized objects. This contrasts with his *inability* to localize sounds in space. He has moderately high myopia without nystagmus and pupil examination was normal. Corrective lenses are worn with difficulty.

3.2. Case 2

3.2.1. Neuroradiology

Non-invasive neuroradiographic evaluation was also performed on the child's father, who was 28 years of age at the time of testing. Magnetic resonance imaging (Fig. 3), demonstrated multiple old bilateral cortical infarctions. Magnetic resonance angiography of the brain (Fig. 4) demonstrated markedly diminished flow in the internal carotid arteries bilaterally. There was no detectable flow in the anterior or middle cerebral arteries, with predominant intracranial blood supply through the basilar artery and middle meningeal arteries. No Moyamoya vessels were

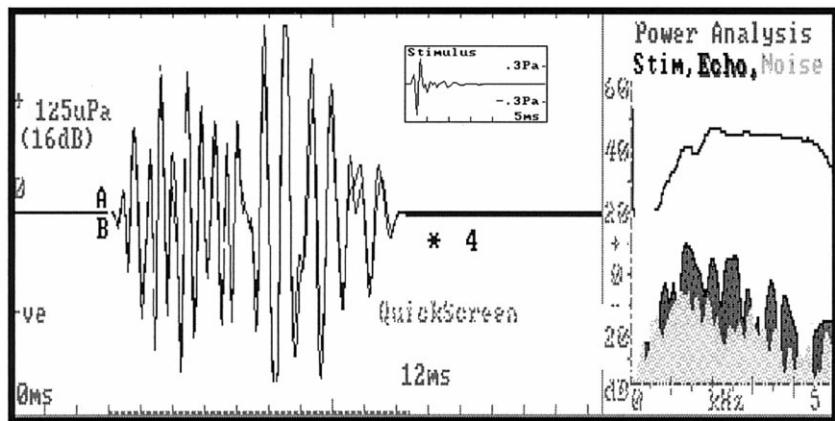


Fig. 5. Top: Example of transient evoked otoacoustic emissions (TEOAEs) obtained from the left ear. Recordings were made using Otodynamics ILO92 hardware and software in the QuickScreen mode. With this method, 80- μ s rectangular pulses were presented at a rate of 50/s, and at a level approximating 80-dB peak sound pressure level (pSPL) through a transducer housed in the ear canal probe assembly. Every fourth stimulus in the stimulus train was presented at a level three times greater in magnitude (9.54 dB), inverted in polarity with respect to the preceding three stimuli, and alternatively sent to one of two separate memory buffers and separately averaged. The input stimulus (insert) and output waveforms are shown on the left side of the panel. The power spectrum (dark grey) and associated noise floor (light grey) areas are shown at the right side of the panel. Bottom: Numerical waveform includes: overall response magnitude in decibels (dB), overall waveform reproducibility in percent (%), one-half octave reproducibility (%), signal-to-noise ratio (SNR) in dB and response stability (%).

detected. This finding corresponds to Stage 6 of the Suzuki classification, which is considered end-stage disease. Selected auditory and visual perceptual testing were also performed.

3.2.2. Behavioral testing

Pure-tone audiometric assessment indicated normal hearing sensitivity from 0.25 to 8 kHz bilaterally (≤ 25 dB HL). We also evaluated aspects of temporal information processing using non-verbal temporal-order tasks in multiple sen-

sory modalities. These measures were performed to determine if deficits in temporal processing are correlated with his learning disability and as such, would provide other information concerning whether processing deficits were modality specific or pansensory in nature.

Stimuli used to assess temporal order performance included frequency and level dimensions in the auditory domain and size, orientation and color dimensions in the visual domain. Examples of the various stimuli are provided in Fig. 9 and a

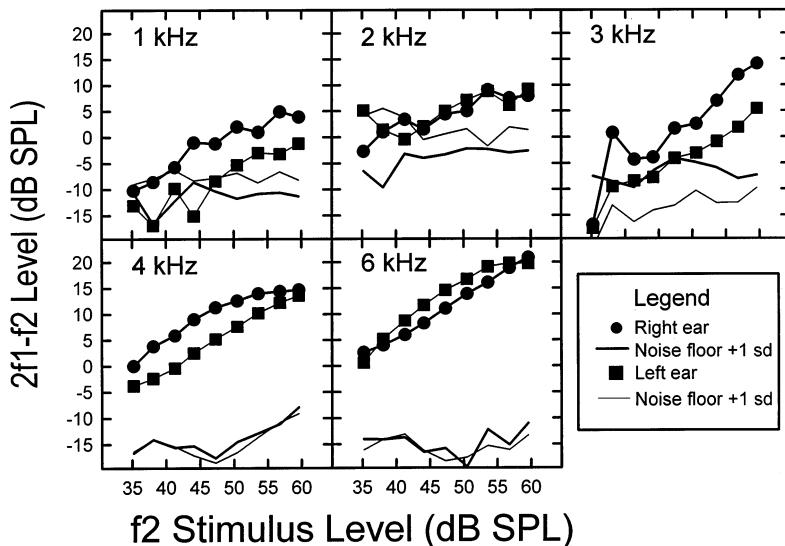


Fig. 6. Distortion product otoacoustic emission growth functions for five f2 frequencies and their associated noise floors. Filled circles represent the right ear and the filled squares represent the left ear. Recordings were made using Otodynamics ILO92 hardware and software. Offset primary levels were used, where f1 was +10 dB greater than f2. The f2/f1 ratio was 1.2.

detailed description of the procedure can be found elsewhere [70]. Briefly, the testing protocol followed a three-interval, three-alternative forced choice (3-IFC) oddity paradigm which was used to generate psychometric functions for each stimulus dimension. The 3-IFC oddity paradigm was selected because it has been applied successfully with a variety of different tasks in both young children and individuals with brain damage [71–73]. It is advantageous in these populations because simple instructions are used (detailed directions concerning relational judgements between stimuli are not required), it provides a criterion-controlled estimate of performance and data are generally robust.

Whereas time did not permit measurement of formal discrimination thresholds (i.e. just noticeable differences (JNDs) for the different stimulus dimensions), it was determined that the participant understood the response requirements of the task. He was clearly able to distinguish relative pitch differences between stimuli (low from high frequency pure tones), relative differences in stimulus level (soft from loud pure tones), and could easily distinguish big from small, horizontal from vertical and yellow from blue.

Based on the psychometric functions obtained on the multimodal temporal order tasks, performance was found to be very poor and never exceeded chance levels (33.3% in a 3-IFC procedure) on any of the stimulus dimensions tested (Fig. 10).

4. Discussion

By the very nature of the disease process and brain areas that become affected, MMD can have devastating effects upon normal development. Herein, we focus on central auditory dysfunction in the context of multiple focal, as well as diffuse CNS lesions, secondary to large vessel cerebrovascular disease. Consideration is given to how these anomalies impair those sensory-perceptual and neuro-cognitive processes necessary for development of verbal-communication abilities in a single child.

In instances where children manifest severe speech and language delay, ruling out peripheral hearing loss is critical to understanding the nature of the problem. In this child, peripheral hearing loss was ruled out by acoustic admittance,

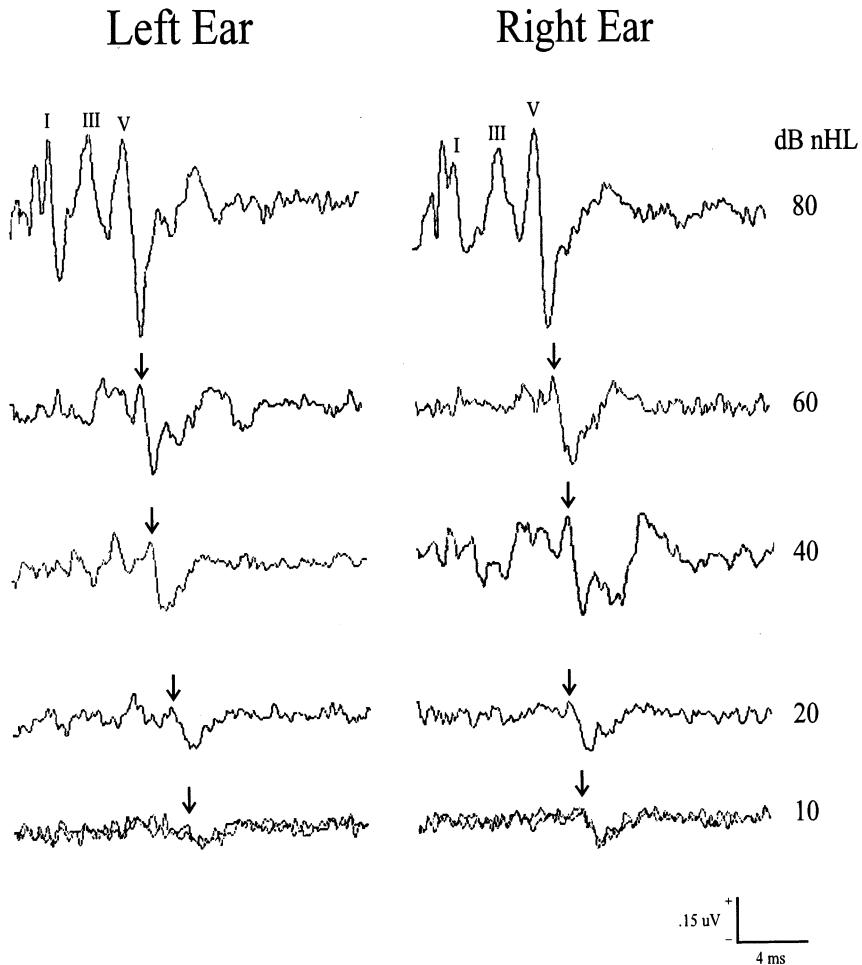


Fig. 7. Brainstem auditory evoked potential waveforms for each ear in response to unfiltered rarefaction clicks, as a function of stimulus level. At high stimulus levels, all waveform components were present and normal. Click thresholds were less than 10 dB nHL, bilaterally. Arrows indicate Wave V identification at low stimulation levels.

TEOAEs, DPOAEs and BAEP measures. The results from these studies provided compelling evidence that the middle ear, sensory receptor and transduction mechanism, as well as the afferent brainstem pathways, were intact and functionally normal through the level of the inferior colliculi (Figs. 5–7) (see [74] for a review of generator sources of auditory brainstem potentials in humans). These physiologic findings are also consistent with MRI data, which indicated that brainstem and cerebellum were structurally normal.

However, further electrophysiologic evaluation demonstrated absent middle and long latency AEPs in the 20–600 ms time frame. Based on pial, intracranial, lesion studies and modeling experiments, these AEP components are thought to have complex generator sources distal to those that generate BAEPs, presumably being thalamocortical in nature (see [67,75,76] for general reviews). Thus, the presence of normal BAEPs and absent middle and LLAEPs indicate that derangement has occurred at a more distal location. Lesion-induced disconnections and various dissociative phenomena, exhibiting different functional

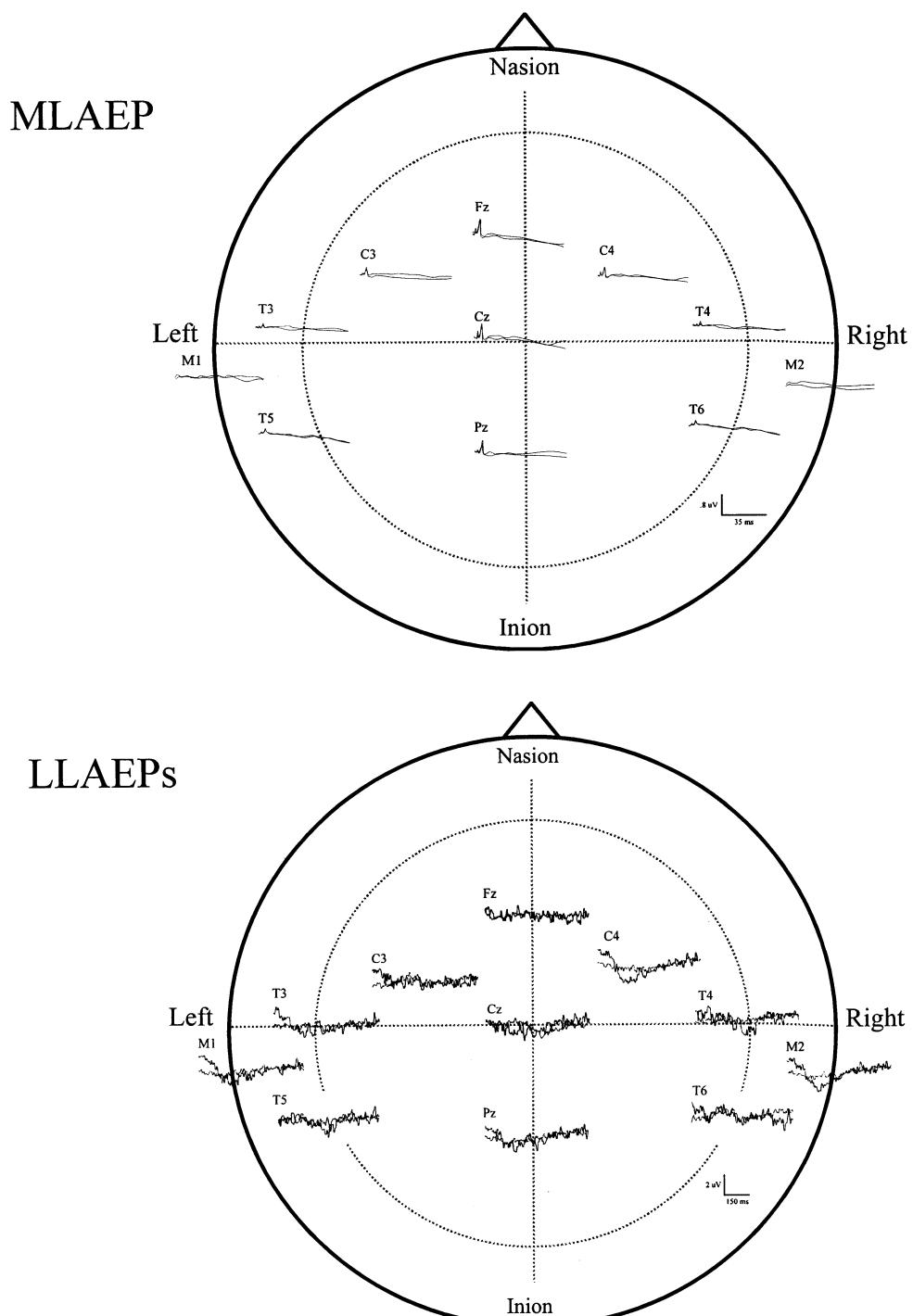


Fig. 8. Top: Recordings of MLAEPs in response to binaurally presented 1000 Hz tone bursts. No MLAEPs were detected at any of the electrode locations. Note the early latency BAEPs. Bottom: Examples of LLAEPs in response to binaurally presented 1000 Hz tone bursts. It is evident that no consistent responses to the standard stimuli were detected across two separate runs at any of the electrode locations.

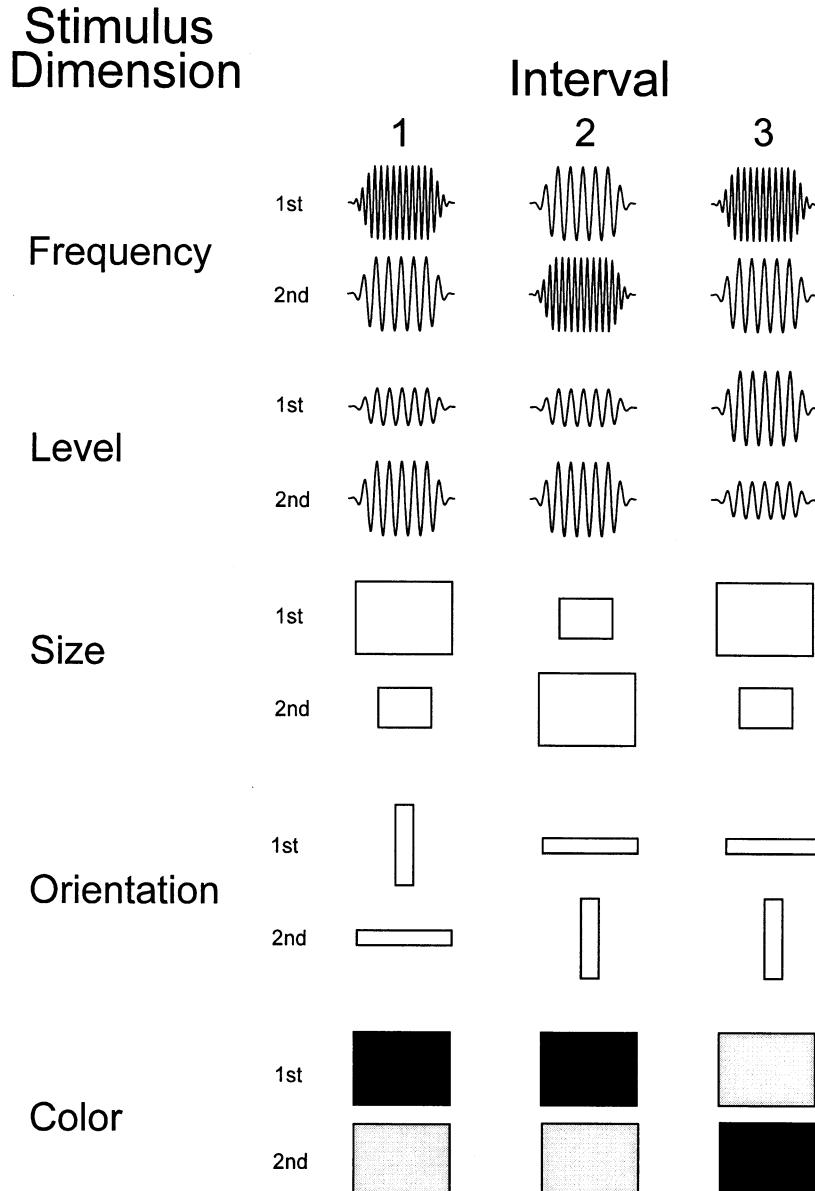


Fig. 9. Examples of auditory and visual stimuli used in the temporal order experiment. Binary frequency patterns consisted of 500 or 1000 Hz pure tones, where stimulus sound pressure level (SPL) 70 dB was held constant. Binary level patterns consisted of 70 or 80 dB SPL pure tones, where stimulus frequency (1000 Hz) was held constant. Binary size patterns consisted of small and large rectangular geometric forms, where the color of the rectangles (white) and the background of the video screen (black) were held constant. Binary orientation patterns consisted of equal sized rectangular bars, where the color (white), background of the video screen (black) were held constant and the orientation of the bars was varied in one of two orthogonal positions: vertical or horizontal. Binary color patterns consisted of different colored rectangles, where the size of the rectangles and the background of the video screen (black), remained constant. The color was changed to appear as either bright blue or bright yellow. These colors were chosen because they could be applicable to a wide range of individuals since yellow/blue color blindness would not be a limiting factor. Because color graphics were not used in this figure, dark filled rectangles correspond to bright blue and light gray filled rectangles correspond to bright yellow colors.

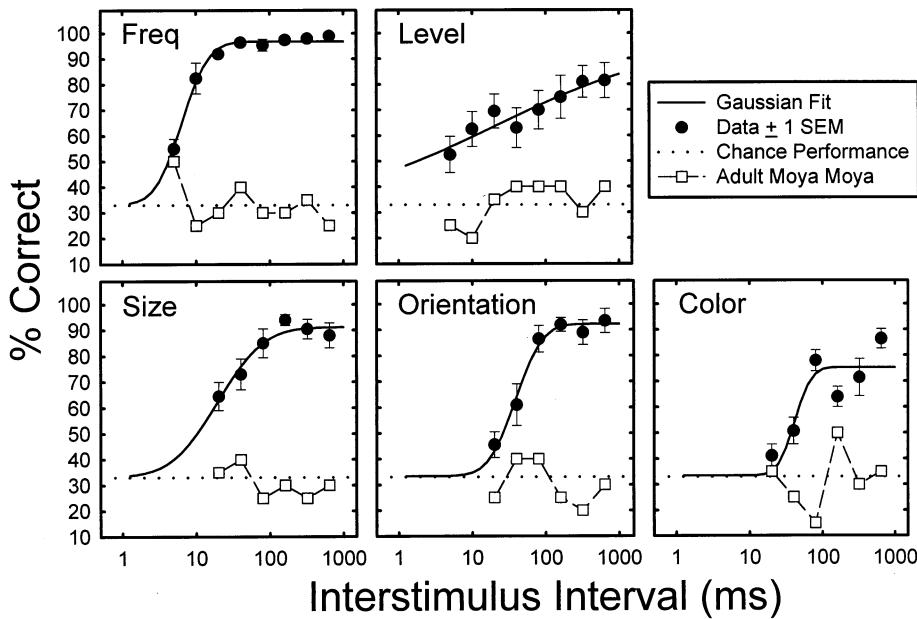


Fig. 10. Average psychometric functions (filled circles) from 10 aged-matched normal control subjects [70] for each of the five stimulus dimensions and for the adult with MMD (open squares). The adult with MMD did not exceed chance performance in the majority of instances. As a result of this poor performance, temporal-order thresholds could not be estimated, but performance clearly deviates significantly from the normal controls.

and electrophysiologic deficits have been observed at all stages of the auditory pathways [76–82]. In the context of cortical deafness, those studies dealing with bilateral temporal lobe lesions are particularly relevant [81–85] because unilateral lesions and other rare dissociative entities, such as word deafness and auditory agnosia typically do not result in the loss of hearing sensitivity.

Tanaka et al. [81] argue that the most severe and persistent forms of so-called 'cortical deafness' occur when bilateral white matter lesions, generally ventral and lateral to the posterior half of the putamen, interrupt all neural projection fibers from the medial geniculate bodies to cortical auditory areas. In two patients with bilateral vascular lesions, Tanaka et al. [81] reported auditory thresholds in the moderately severe-to-profound range, intact BAEPs (Waves I–VI) and complete absence of middle latency component Pa bilaterally. Interesting, the LLAEP (N1P2 complex) were preserved in both cases. In another well-documented case of 'cortical deafness', bilateral subcortical hemorrhages localized to a region ven-

tral and lateral to the putamen were also documented [90]. Özdamar et al. [78] report a case of cortical deafness with preserved BAEPs but absent middle latency peaks Pa. Based on CT studies, Özdamar and colleagues concluded that the absence of the MLAEP component Pa was due to hematomas and infarcts of the left and right temporal lobes. However, secondary changes in thalamic projections as a cause for this abnormality was not ruled out. Woods et al. [82] reported a case of cortical deafness in an 82-year-old-woman, resulting from successive strokes of the right and left temporal lobes secondary to bilateral occlusion of the posterior temporal branch of the middle cerebral arteries. Whereas pure tone behavioral thresholds were in the moderate-to-profound range and no auditory discriminations could be made, middle and long latency AEPs (P1, N1, P2) were preserved. This case dissociated perception from the generation of middle and LLAEPs. In a review of other cases with bitemporal lesions of the auditory cortex which did not produce cortical deafness, Woods et al. [76] were

unable to support the view that the primary generator sources of middle and LLAEPs reside exclusively in auditory cortex. They suggest that abnormalities found in MLAEPs are associated with subcortical lesions or cortical lesions extensive enough to denervate thalamic projection nuclei and that abnormalities in the long latency N1 component recorded from central scalp locations reflect lesion extension into multi-modal areas of the inferior parietal lobe.

The results obtained from our child differ from the above mentioned studies because both middle and LLAEP components were absent. Toyoda et al. [92] suggest that large vessel vascular disease, including those with moyamoya-like vasculopathies, significantly affects auditory evoked magnetoencephalographic (MEG) fields and dipole source localization in the middle latency range. Toyoda and colleagues also correlated MEG abnormalities with changes in blood flow based on positron emission tomography (PET) and showed that reduced perfusion in areas encompassing both the auditory radiations and auditory cortex correlated with the deficits in the auditory evoked magnetic fields. In the child of this report, angiography showed that the middle cerebral artery was absent on the right side and almost completely occluded on the left side, except for a prominent angular/parietal branch. The absence and occlusion of these vessels is significant because they supply blood to the lateral two-thirds of each hemisphere (motor, tactile and auditory areas) as well as to adjacent subcortical sites [86]. From a functional standpoint, it is reasonable to suggest that subcortical and cortical ischemic damage and other focal lesions in frontal, parietal and temporal lobes, resulted in the evoked potential abnormalities and the lack of localization behaviors to sound (Figs. 1 and 2). Lesions to the frontal cortex present in this child, can also impair generation of MMN [91]. Taken together, the behavioral and electrophysiological abnormalities are consistent with a diagnosis of central deafness. Furthermore, it is assumed that these lesions also disrupted normal development by impairing information transfer within neuro-cognitive networks necessary for various attentional, language and memory processes [87–89].

Thus, the combination of behavioral, electrophysiologic and functional neuroimaging studies are necessary to define central auditory disorders in both adults and children, since one cannot rely exclusively on AEP studies alone to validate the functional integrity of primary and secondary auditory cortices. In this regard, further research in this area is needed to better parcellate various AEP components over central and lateral temporal lobe locations [67,93] and to correlate these results with functional deficits. In comparison to scalp-recorded EEG-based assessment of sound evoked activity generated in auditory cortex, MEG is advantageous because it is relatively unaffected by the inhomogeneities (i.e. smearing effects) of the skull. However, MEG is insensitive to radial dipole sources, and therefore cannot provide a complete representation of auditory cortex integrity. In this regard, methods which can parcellate both tangential and radial dipole activities need further attention. These include dipole source potentials based on specific models [94,95] and spatial filtering techniques, which can also delineate global from more local activations (i.e. activity over lateral temporal lobe sites). This latter approach may be easier to implement because it does not require model-dependent assumptions [96,97].

To our knowledge, only one other case of central deafness, secondary to MMD, has been reported in the literature ([98], cited by [81]). Although the prevalence of central deafness in children with MMD is not known, we suspect that it may not be a common manifestation. More than likely, speech, language, central auditory and cognitive disturbances associated with MMD will fall along a continuum of severity and will be dependent on age-of-onset, severity of deficits, extent of collateral circulation and the type and success of treatment [59,60,99]. With respect to verbal communication abilities, one detailed case study [100] describes persistent expressive speech difficulties, short attention span, and psycholinguistic deficits. In this case, hearing sensitivity was basically unaffected. The bilateral nature of MMD contrasts with children who have unilateral cortical damage early in life, where development of receptive and expressive communicative pro-

cesses is much different and perhaps where outcome measures are more optimistic. For example, in a comprehensive longitudinal study, it has been shown that children with unilateral brain damage incurred before 6 months of age can achieve normal language skills with little or no evidence of detectable language impairment by 5–6 years of age [101]. The implication from this research is that regardless of which hemisphere is affected, when damage occurs early in life other brain areas can assume language functions. What complicates this issue is that little is actually known about the development and/or representation of cortical language organization in children [102–105] and the fact that issues related to language acquisition and use and theoretical perspectives on neurolinguistic development are still evolving [106,107].

These functional results can be much different in individuals who are diagnosed later in life. In a case report of a 19-year-old female with MMD, normal function was observed on a large number of neuropsychological tests including tests of abstract reasoning, and memory [60]. This example emphasizes that not all cases of MMD lead to devastating consequences. Other studies have shown significant deficits in both central auditory and visual information processing, with normal pure tone thresholds [108]. In the present study, this 28-year-old gentleman is not incapacitated by the disease. He functions without difficulty in activities of daily living, has obtained a special high-school diploma, but has been unable to secure employment. No doubt, his global learning disability (5th grade reading skills; 3rd grade math skills) has limited his employment opportunities in the small semi-rural community where he resides. Like the other two cases reported above, he performs simple threshold-detection tasks without difficulty and has normal pure tone hearing sensitivity bilaterally. However, he was significantly impaired on more complex tests that require the ability to discriminate the order of rapidly presented events in time (Fig. 10). His performance on these tasks was at chance levels in all modalities, which contrasts to the highly accurate performance we have observed in adults of similar age without learning disabilities [70]. Furthermore, normally developing children (9–11 years of age)

without any academic problems, can also have adult-like performance on these multi-modal temporal-order tasks. In contrast, children with reading-based learning impairments have pansensory performance deficits like those observed in the adult with MMD [109].

The temporal order deficits observed in this adult with MMD may share some relationship to proposals that emphasize the role of timing in neural processing [110]. Although correlations between temporal-order deficits and a variety of acquired neurological dysfunctions have been reported, cause-and-effect relationships are not always straightforward [110–115].

In Caucasian families with no evidence of Japanese ancestry, the incidence of MMD is very low and to our knowledge, the occurrence of central deafness in children with this disease has not been reported in the literature. Kitahara et al. [31] identified the familial incidence of MMD in three Japanese families to be more than 12%. In families with a positive history of MMD, Houkin et al. [30] estimate that the frequency of occurrence in offspring is between 6 and 9%. Yamauchi et al. [32] showed an incidence of 3% among siblings and 80% in monozygotic twins. These data support other research findings suggesting that this disease has a tendency to show multifactorial inheritance. Other reports which suggest a congenital (genetic or environmental) influence are based in part on identical twins studies and other cases of MMD associated with persistent primitive trigeminal artery variant (see [19] for a detailed discussion). What distinguish our cases from other reports in the literature are the absence of Japanese ancestry and the presence of paternal linkage. The paternal linkage of MMD in this case is both noteworthy and significant because it rules out x-linked recessive and maternal inheritance.

5. Conclusion

Moyamoya disease is a rare, progressive and occlusive cerebrovascular disorder which predominantly affects the carotid artery system. The significant delay in speech and language

development was the main impetus for pursuing comprehensive auditory studies, leading to the presumed diagnosis of central deafness. This study comprehensively documents, with contemporary methods, a unique profile of auditory findings characterized by normal acoustic admittance, OAEs and BAEPs and absent MLAEPS and LLAEPS. The absent middle and LLAEPS correlate with the abnormal behavioral responses on standard sound-field testing. Whereas the EDAS procedure was successful in halting the progression of the disease (cessation of TIAs and strokes), to date, it has not resulted in reversing existing neurological deficits, although we do not know if improvements will occur as the child develops. It appears that a combination of subcortical white matter and cortical ischemic damage, in addition to multiple and focal cerebral infarctions localized in frontal, parietal and temporal lobes result in severe auditory dysfunction. It is inferred that lesions of this nature will also negatively influence memory and attentional processes necessary for speech and language development. Comprehensively documenting functional deficits with contemporary methods and determining how they interact with age-of-onset and type-of-treatment, are important outcome measures which are needed to allow healthcare workers and researchers to: (1) better understand the nature of the disease process, (2) improve treatments and, (3) allow effective counseling of parents with realistic expectations regarding quality-of-life issues.

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