

A Syndrome of Brain, Inner Ear and Retinal Microangiopathy

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ABSTRACT: We report the seventh case of a self-limiting syndrome of brain, inner ear and retinal microangiopathy which affects adult women producing mild to moderate mental status and personality changes, mild pyramidal and cerebellar dysfunction, patchy and asymmetrical visual loss secondary to non-inflammatory retinal infarctions, and asymmetrical neurosensory hearing loss. There is no clinical or laboratory evidence of involvement beyond the brain, the eyes and the ears. Magnetic resonance imaging or brain biopsy in previously reported cases best outline the brain pathology: multiple microinfarcts. All cases have been treated with steroids or cyclophosphamide. The etiology is unknown but may be related to systemic lupus erythematosus.

RÉSUMÉ: Micro-angiopathies localisées au cerveau, à l'oreille interne et à la rétine. Nous rapportons le septième cas d'un syndrome comportant des micro-angiopathies à localisation bien circonscrite, soit au niveau du cerveau, de l'oreille interne et de la rétine. Ce syndrome atteignant les femmes d'âge adulte, provoque une altération de légère à modérée de l'état mental, des modifications de la personnalité, une légère dysfonction pyramidale et cérébelleuse, une perte de vision en plaques disséminées et asymétrique qui est secondaire à des infarctissements rétiens non-inflammatoires et une surdité neurosensorielle asymétrique. Aucune atteinte autre qu'au cerveau, aux yeux et aux oreilles ne peut être mise en évidence par la clinique ou les examens de laboratoire. L'imagerie par résonance magnétique ou la biopsie cérébrale sont les deux examens qui démontrent le mieux la pathologie cérébrale sous-jacente à cette entité, soit les nombreux micro-infarctus. Tous les cas ont été traités au moyen de stéroïdes ou de cyclophosphamide. L'étiologie de ce syndrome est inconnue, mais elle pourrait être reliée au lupus érythémateux aigu disséminé.

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To date six patients, all young women, have been described with a remarkably similar and distinctive syndrome of retinal arteriolar infarction, neurosensory hearing loss especially in the lower frequencies (presumably due to infarction of the cochlear apex), and small multifocal central nervous system white and grey matter infarcts. The course of the disease seems to be biphasic or multiphasic with a duration of several months followed by partial recovery and a lengthy remission. The first two cases were described in 1979 by Susac et al.¹ Two cases were reported by Coppeto et al.² in 1984 and two by Monteiro et al.³ in 1985. The following case is another example of this syndrome.

CASE REPORT

A 31 year old pregnant woman (para III, gravida IV) developed intermittent numbness of all four extremities in March 1981 followed by slurring of speech. In late April she noted a persistent "blind spot" in the left eye. Her corrected visual acuity was 20/20. She had an exophoria on near vision and an area of left retinal infarction just superior to the macula within the area of supply of a cilioretinal artery. Goldman perimetry revealed two dense scotomas both at about 20° of nasal

eccentricity — one above and one below the horizontal meridian. One week later she developed horizontal diplopia and was found to have a left sixth nerve palsy confirmed on a Hess test.

In mid May she complained of lethargy, general malaise, unsteadiness of gait and had become noticeably less animated in her personality and less proficient in memory. She noted right ear tinnitus and a localized skin eruption on the right cheek. Her blood pressure was 95/65. There was a one inch diameter erythematous papulo-vesicular skin eruption on the right lower cheek. She was alert, oriented, dysarthric, flat in affect and frequently referred to her husband for confirmation of her answers, but had no defect in memory and no dysphasia. The left optic disc was pale; the peripheral visual fields were intact and visual acuity was 20/20. Extra ocular movements were full, the abductors palsy having disappeared, and there was no nystagmus. The remainder of the cranial nerves were intact with normal Rinné and Weber tests. Muscle power, coordination and fine movements in the upper limbs were normal. There was a spastic catch upon elbow flexion bilaterally. Ordinary gait was normal but heel-toe walking and heel-knee testing were ataxic. Deep and superficial sensations were intact. Upper limb tendon reflexes were normal. The knee jerks were hyperactive with a Babinski reflex bilaterally and the abdominal reflexes were absent. The infarction edema in the left retina had subsided.

The patient's speech, memory, affect and ataxia improved without specific treatment but bilateral tinnitus developed and a bilateral low frequency neurosensory hearing loss, left greater than right (40 to 10 decibels threshold from 250-8000 Hz), was detected. In November 1981

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she delivered a normal baby without complications but fatigue, dysarthria, incoordination in writing and gait and difficulty with memory reappeared. Her left hearing suddenly deteriorated (Figure 1).

In January 1982 because of persistent symptoms she was again admitted. Her physical signs and laboratory findings were unchanged. It was concluded that she was suffering from a type of vasculitis and she was started on prednisone, initially 60 mg/day. Her speech, memory and "dizziness" improved.

She noted a further left visual loss in March 1982 following which her V.A. was 20/20 o.d. and 20/400 o.s., with correction. There were four small intraretinal hemorrhages and marked adjacent artery narrowing in the left retina with a retinal infarct below the left macula. Perivascular sheathing and artery narrowing were also present in the right retina. Visual fields (Goldman) showed a central scotoma and a quadrantic left superior nasal depression. There was a peripheral infero-temporal defect in the right visual field and a left afferent pupil defect. Prednisone was increased to 30 mg per day. By August 1982 her vision had improved to 20/20 (with correction) but a left paracentral scotoma remained. Her prednisone was slowly reduced and then stopped.

In November 1985 pure tone audiometry was abnormal bilaterally but slightly improved in the right ear over her previous maximum deficit (Figure 1). 100-Hue color vision testing revealed abnormal scores bilaterally: R = 197, L = 320 (normal score for age @ $p = 0.01 = 154$)⁴. When last seen in January 1987, nearly six years after the onset of her illness, she was on no medication and was feeling well except for fatigue, slurring of speech, some short term memory difficulty, and diminished hearing, left greater than right. V.A. was 20/20 with correction. Octopus perimetry (Program G1) showed a patchy diffuse loss of retinal sensitivity bilaterally with a left paracentral scotoma. Neurological examination was normal except for clumsiness in hopping, hyperac-

tive knee and right ankle reflexes and an equivocal left plantar reflex. Laboratory studies are as summarized in Table 1.

DISCUSSION

The salient features of the six previously reported cases and this case are remarkably similar (Table 2). All are female, age 21-40, in whom the disease usually begins with personality or mental status changes including flattening of affect, memory loss, dementia, paranoia, obtundation. Simultaneously or very soon after the onset the other cardinal features appear, namely asymmetrical neurosensory hearing loss most marked in the low and middle frequencies, asymmetrical visual loss secondary to multiple retinal artery branch occlusions, and infarctions and relatively mild symptoms and signs of motor and cerebellar dysfunction. After a subacute course over a period of several months and sometimes with a biphasic course, there is a remission, with no subsequent exacerbation, leaving a residual mild to moderate mental status change and asymmetric hearing loss and visual changes. Extensive laboratory investigation to detect abnormalities beyond the eye, ear and brain is unrewarding, confirming the specificity of the pathology to the brain and these special sense organs. Consistent nervous system abnormalities include diffuse theta and delta activity on the EEG and an elevated CSF protein occasionally with a slight CSF

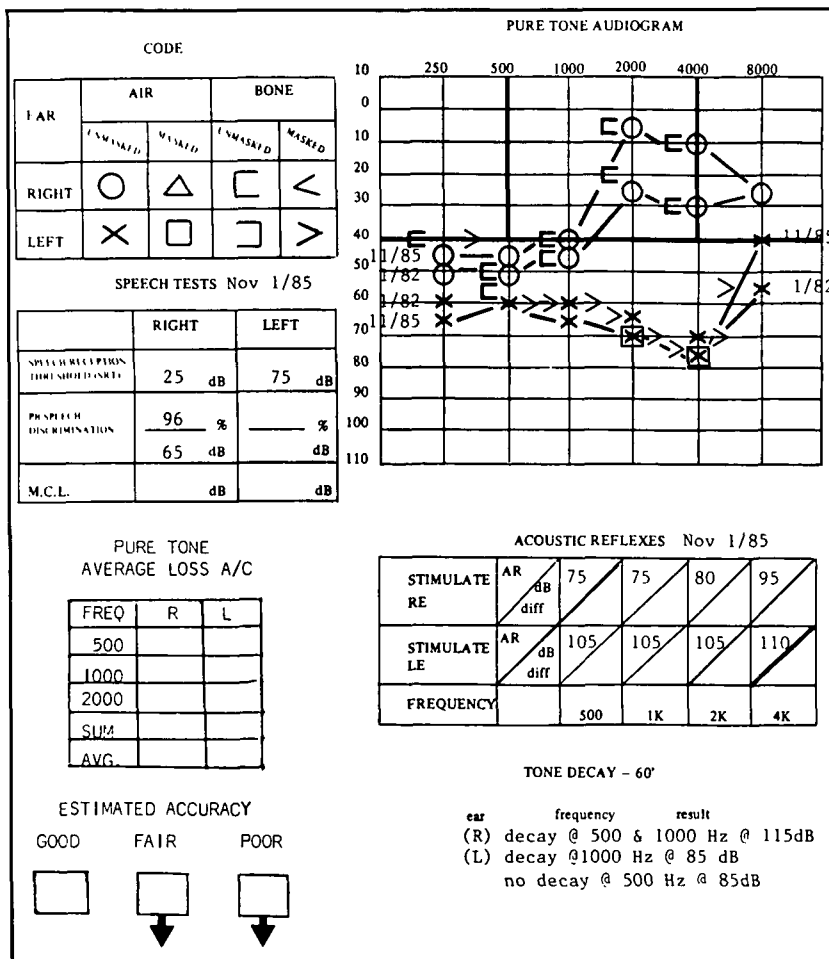


Figure 1 — Pure tone audiogram of January/82 and November/85 which illustrate the low frequency hearing loss and modest improvement between the two tests. Speech tests and acoustic reflexes of November/85 are also shown.

lymphocytosis. Two patients have undergone a brain biopsy. In one "sclerosis of the media and adventitia of small pial and cortical vessels" consistent with a "healed angiitis" was found,¹ and in the other there were "numerous microinfarcts throughout the gray matter" with "no evidence of inflammation" or "fibrinoid necrosis of vessel walls".³ CT scanning of the brain reveals no abnormalities and, at most, cerebral angiography has revealed questionable "small vessel abnormalities".¹ Magnetic resonance imaging (MRI) of the brain in one patient³ showed "several high intensity foci — only in the white matter — compatible with small brain infarcts."

It seems clear from the ophthalmological findings that the visual abnormalities are the result of an arterial angiopathy which is not inflammatory, atherosclerotic nor likely embolic in nature. The brain biopsy and MRI findings outlined above are consistent with the ophthalmological findings. The inner ear pathology is unknown but is consistent with infarction of the cochlear apex, thus accounting for the predominantly low and middle frequency neurosensory hearing loss.

All patients were treated with corticosteroids or ACTH and three with cyclophosphamide. The effectiveness of this treatment is unclear as some patients had transient clinical improvement prior to the institution of therapy and all patients recovered partially from their initial central nervous system, visual and auditory symptoms.

The differential diagnosis has been extensively discussed in the three previous reports^{1,2,3} and includes polyarteritis nodosa, allergic vasculitis, giant cell granulomatous angiitis of the nervous system, atypical Cogan's syndrome and systemic lupus

erythematosus (SLE). The neurologic and retinal findings in these seven cases are not characteristic of even atypical Cogan's syndrome³ and therefore only SLE seems a serious consideration. Laboratory support for the diagnosis of SLE in these patients is lacking and our patient had only one of the 11 criteria used in the diagnosis of SLE,⁷ namely "neurologic disorder". Nevertheless, that these cases may represent a sero-negative "cerebral" type of SLE remains a possibility. Coppeto et al² described their two cases as a "syndrome of arterial occlusive retinopathy and encephalopathy", did not elaborate upon the hearing loss in their two patients and included, as further examples of this syndrome, two patients without hearing loss described by Pfaffenbach and Hollenhorst⁵ and considered by them to be examples of probable SLE. Montero et al³ who emphasized the hearing loss in their two cases and in the previous four cases, "suspected" that the two patients of Pfaffenbach and Hollenhorst had "partial" manifestations of (this) microangiopathic syndrome" and similarly categorized a single patient described by Weidhauer and Tenner⁶ in which a young woman had bilateral neurosensory hearing loss, retinal artery branch occlusions but no central nervous system or systemic involvement.

This microangiopathic syndrome of arteries which appears to be unrelated to emboli, vasculitis or SLE might be related to a defect in coagulation such as occurs in the presence of lupus anticoagulant where thrombosis exceeds bleeding. Furthermore, lupus anticoagulant occurs more often in those without SLE than in those with it.⁸ Thus a search for a coagulation abnormality during the acute stage of this syndrome might help to clarify the etiology.

Table 1: Results of laboratory investigations during "acute" stage

Abnormal results	Normal results
ESR — May/81: 41 mm/hr; Feb/82: 58 mm/hr.	Urine — urinalysis, amino acids
Antinuclear factor — positive May/81: 1/40, speckled pattern Feb/82: 1/30, speckled pattern.	Blood/serum — Hgb, MCV, MCH, wbc count, differential, platelet count, electrolytes, total protein, protein electrophoresis, Ca, PO ₄ , uric acid, alkaline phosphatase, total bilirubin, CPK, LDH, SGOT, fasting blood sugar, urea, VDRL (May/81), RST (Feb/82), B12, folate, iron, lead, arsenic, copper ceruloplasmin.
CSF — May/81: 192 rbc/cmm, 0 wbc/cmm, protein 252 mg%, glucose 53 mgm%, gram stain and culture negative, cryptococcus LA test negative, no oligoclonal banding. — Jan/82: 10 rbc/cmm, 0 wbc/cmm, protein 116 mg%, glucose 37 mgm%, reagin screening test (RST) non-reactive.	Coagulation studies not done.
EEG — May/81: intermittent bilateral fronto-temporal delta activity.	Antibodies — mitochondrial, smooth muscle, ribonucleoprotein, Smith, anti-nuclear factor (Jan & Mar/82).
VER — Jan/82: latency: (L) = 218 msec, (R) = 208 msec.	BAER — May/81
BAER — Jan/82: increased hearing threshold of 50 dB (L) ear, 10 dB (R) ear as compared to May/81 and a 0.5 msec. latency delay in Wave I (L) as compared to (R).	Imaging — chest X-ray, CT scan with delayed double contrast, Tc scan of liver and spleen, Tc scan of brain.
	Biopsies — skin, rectal mucosa, skeletal muscle, temporal artery.
	Viral serology — Jan & Mar/82) cytomegalo-virus, varicella, herpes simplex, measles, influenza A.
Additional investigation: (Jan/87) all normal: T3, T4, TSH, ESR, prothrombin time, PTT, thrombin time, bleeding time, Factor XII, antithrombin III activity, fibrinogen time, anti-SS-A&B.	
Investigations not done: cerebral angiography, cerebral biopsy, MRI of brain, ultrasound of heart and neck vessels.	

Table 2: Comparative features of this and six previously reported cases^{1,2,3}

	MacFadyen et al	Previous cases
Sex	female	all female
Age	31	21 - 40
Initial symptoms	numbness of extremities, dysarthria	personality or mental status changes (5/6), hearing loss (2/6), fever, headache, ataxia and vomiting (1/6), dysarthria (1/6)
Subsequent symptoms	(L) scotoma, personality change, memory loss, tinnitus, bilateral hearing loss, further (L) visual loss	ataxia (3/6), dementia (1/6), memory loss (3/6), obtundation (1/6), mood/personality changes (1/6), dysarthria (2/6), hearing loss (3/6), visual loss bilateral (2/6), unilateral (2/6)
Neurologic findings	dysarthria, (L) V1th palsy, ataxia, hyper-reflexia, bilateral Babinski, normal sensation	gaze palsy (1/6), ataxia (3/6), hyper-reflexia or Babinski (5/6), grasp reflex (2/6), nystagmus (2/6), normal sensation (3/3)
Cerebral/mental changes	personality change, memory loss	amnesia or disorientation (1/6), paranoia (2/6), personality change (2/6), seizures and obtundation (1/6)
Visual findings		
— visual acuity	<20/30 unilateral	<20/30 unilaterally (1/6), <20/30 bilaterally (1/6)
— retina	focal retinal infarcts, small hemorrhages, arterial occlusion, arterial narrowing, perivascular sheathing	retinal infarcts (6/6), retinal hemorrhages (1/6), inflammatory changes including vitreous, uvea (0/6), arterial narrowing (6/6), arterial occlusion (6/6)
Audiometric findings	bilateral low-frequency neurosensory loss: asymmetric BAER: unilateral abnormality	bilateral asymmetric neurosensory loss (5/6); hearing loss but no audiometry (1/6) normal (2/6), unknown (4/6)
EEG	intermittent bilateral frontotemporal delta	generalized dysrhythmia or bilateral slow activity (5/6), normal (1/6)
CT scan	normal	normal (6/6)
Brain MRI	not done	“several small discrete foci of abnormally high signal intensity throughout the supratentorial white matter” (1/6)
Abnormal laboratory findings	elevated CSF protein, elevated ESR, + ANF (1/30 & 1/40)	CSF: elevated protein (5/6), 12 - 17 lymphocytes (2/6); elevated ESR (1/6)
Brain biopsy	not done	microinfarcts in grey matter (1/6), “healed angiitis” (1/6)
Echocardiography	not done	normal (4/6)
Treatment	prednisone	prednisone/hydrocortisone/dexamethasone (6/6), cyclophosphamide (3/6)
Follow-up	hyper-reflexia, visual field defects, asymmetric hearing loss: unchanged after six years	moderate to mild dementia (4/6), hyper-reflexia (4/6), hearing and visual loss (4/6; 2/6 unknown)

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