Small Infarctions of Cochlear, Retinal, and Encephalic Tissue in Young Women

J. Schwitter, MD; R. Agosti, MD; P. Ott, MD; A. Kalman, MD; and W. Waespe, MD

Background and Purpose: Recently, a rare syndrome that involves uniformly the brain, inner ear, and retina in previously healthy young women has been described. Brain biopsies and ophthalmologic examinations disclosed small infaracts as a pathoanatomical substrate of the disease. In previous reports, an autoimmune disorder or a coagulopathy have been suggested as possible etiologies.

Case Descriptions: Both patients (aged 22 and 20 years) had brain involvement with neurological and neuropsychological deficits. Multifocal small hyperintensities were shown in magnetic resonance imaging of the brain. Findings of cerebrospinal fluid examination and electroencephalography were pathological in case 1 and of cerebral angiography in case 2. Both patients had a neurosensory hearing loss and multiple retinal branch arteriolar occlusions. Both women were on fenfluramine before onset of the disease. In case 1, attacks recurred during a follow-up of 34 months. At onset of the disease the 5-hydroxyindoleacetic acid and homovanillic acid levels of the cerebrospinal fluid were reduced; 13 months later the 5-hydroxyindoleacetic acid level was still reduced and the homovanillic acid level was low-normal. In case 2, with the longest follow-up of 13 years, the disease was active during only the initial 2½ years. During this period a combination of oral anticoagulant and antiplatelet agents was ineffective.

Conclusions: Our findings could not support current etiologic hypotheses. Whether changes in 5-hydroxyindoleacetic acid and homovanillic acid levels in the cerebrospinal fluid and/or fenfluramine intake play a role in the pathogenesis of the disease remains to be elucidated. (Stroke 1992;23:903–907)

KEY WORDS • cerebral infarction • dementia • hearing loss • retinal artery • young adults • women

Since the first report of two psychotic patients in 1979,1 to our knowledge 14 other young women who were all affected by an encephalopathy, neurosensory hearing loss, and retinal arterial occlusions have been described.1-8 We describe two additional patients with this syndrome.

Case Reports

Case 1

A 22-year-old woman was well until the summer of 1988, when her employer, a general practitioner, noticed subtle personality changes. In 1987 she took the anorectic drug d-fenfluramine (30 mg/day) for 3 weeks; in the spring of 1988, for 1 week (30 mg/day). During the first half of 1988 she used oral contraceptives. She did not smoke. In November 1988 a severe neurosensory hearing loss occurred in her right ear; in April 1989 another one occurred in her left ear.

At admission to the hospital, a general physical examination was normal as was an electrocardiogram (ECG), chest roentgenogram, routine blood and urine work (including cultures), serological tests, evoked potentials, calorimetry, and a computed tomogram (CT scan) of the brain. During the following days the patient's memory worsened, especially for figural information. There was a marked constructional apraxia and difficulties with concept identification and interference control. She was depressed. Neurological examination disclosed a severely ataxic gait, a horizontal left-beating nystagmus, and hyperactive tendon reflexes. Magnetic resonance imaging (MRI) of the brain showed disseminated small gadolinium-enhancing hyperintensities in the white and gray matter (Figure 1). Cerebrospinal fluid (CSF) had 2 lymphocytes/mm³ and an increased protein content (620 mg/l). IgG index was normal, with no oligoclonal bands. CSF cultures were negative. The 5-hydroxyindoleacetic acid (HIAA) and homovanillic acid (HVA) levels in the cerebrospinal fluid and/or fenfluramine intake play a role in the pathogenesis of the disease remains to be elucidated. (Stroke 1992;23:903–907)

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FIGURE 1. Magnetic resonance images of patient 1 in April 1989. Left: In T$_{2}$-weighted scan (echo time [TE] 20 msec, resonance time [TR] 550 msec) several hyperintense foci are scattered throughout cerebellum and pons. Gadolinium enhancement of lesions gives evidence for disturbances of blood–brain barrier. Right: T$_{2}$-weighted scan (TE 40 msec; TR 2,500 msec) through basal ganglia region shows additional bilateral small hyperintensities.

(Figure 2, Table 1). A contrast echocardiogram and an angiogram of the aortic arch and the cerebral circulation were normal. The patient was prescribed an antiplatelet agent (aloxiprin, 600 mg/day). After a symptom-free interval of 8 weeks, a detailed coagulation profile (including anticardiolipin antibodies [ACA]) was normal. Later the same day a right-sided neurosensory hearing loss occurred.

In May 1990, while still taking aloxiprin, the patient awoke with a disabling vertigo. A spontaneous right-beating horizontal nystagmus was present. Caloric responses were absent on the right side and severely reduced on the left side. MRI of the brain showed no new foci but a diffuse slight increase of signal intensity in the white matter. In CSF the level of HIAA was again severely reduced (2 nmol/l) and the HVA level was

FIGURE 2. Fluorescein angiography of left eye of patient 1 in January 1990 shows multiple branch retinal arteriolar occlusions (arrows).
<table>
<thead>
<tr>
<th>Brain involvement</th>
<th>Present cases</th>
<th>Total cases (N=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unsteady gait</td>
<td>+ 14 15 93</td>
<td></td>
</tr>
<tr>
<td>Hyperactive tendon reflexes</td>
<td>+ 12 15 80</td>
<td></td>
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<tr>
<td>Babinski’s sign</td>
<td>- 11 15 73</td>
<td></td>
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<tr>
<td>Dysmetria</td>
<td>- 7 15 47</td>
<td></td>
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<tr>
<td>Dysarthria</td>
<td>- 7 15 47</td>
<td></td>
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<tr>
<td>Nystagmus†</td>
<td>+ 6 15 40</td>
<td></td>
</tr>
<tr>
<td>Gaze palsy, VI, VII nerve palsy, diplopia</td>
<td>- 4 15 27</td>
<td></td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>- 4 15 27</td>
<td></td>
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<tr>
<td>Paresthesia, hypesthesia</td>
<td>+ 4 15 27</td>
<td></td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>+ 3 15 20</td>
<td></td>
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<tr>
<td>Paresis</td>
<td>- 3 15 20</td>
<td></td>
</tr>
<tr>
<td>Seizures</td>
<td>- 2 15 13</td>
<td></td>
</tr>
<tr>
<td>Personality and behavioral disturbances</td>
<td>+ 9 15 60</td>
<td></td>
</tr>
<tr>
<td>Paranoid, aggressive</td>
<td>- 4 15 27</td>
<td></td>
</tr>
<tr>
<td>Euphoric, anosognostic</td>
<td>- 3 15 20</td>
<td></td>
</tr>
<tr>
<td>Depressive</td>
<td>+ 4 15 27</td>
<td></td>
</tr>
<tr>
<td>Cognitive dysfunction</td>
<td>+ 9 15 60</td>
<td></td>
</tr>
<tr>
<td>Memory loss</td>
<td>+ 9 15 60</td>
<td></td>
</tr>
<tr>
<td>Confusion</td>
<td>- 8 15 53</td>
<td></td>
</tr>
<tr>
<td>Lethargy, apathy</td>
<td>- 7 15 47</td>
<td></td>
</tr>
<tr>
<td>Dementia (end stage)</td>
<td>- 4 15 27</td>
<td></td>
</tr>
<tr>
<td>Mild-moderate</td>
<td>- 1 15 7</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>- - 15</td>
<td>7</td>
</tr>
<tr>
<td>Multiple focal cerebral and cerebellar areas of high signal intensities</td>
<td>+ + 9 10 90</td>
<td></td>
</tr>
<tr>
<td>(white/gray matter) on magnetic resonance imaging</td>
<td>+ + 9 10 90</td>
<td></td>
</tr>
</tbody>
</table>

### Cerebrospinal fluid

- Elevated protein content
  - + 15 17 88
- Pleocytosis (predominant lymphocytosis)
  - + 9 14 64
- IgG index slightly elevated
  - - 3 17 18
- Generalized dysrhythmia, diffuse slowing on electroencephalogram
  - - 10 12 83
- Atrophy on computed tomogram
  - - 4 12 33
- Small vessel involvement on cerebral angiography
  - + 2 12 17
- Microinfarcts (white/gray matter) on brain biopsy
  - - 4§ 4 100

### Ear involvement

- Hearing loss
  - + 18 18 100
- Neurosensory (audiogram)
  - + 14 14 100
- Bilateral
  - + 10 14 71
- Low/medium frequencies
  - + 5 7 71
- Vestibular dysfunction (caloric response)
  - - 2 4 50

### Eye involvement

- Retinal branch arteriolar occlusions
  - + 18 18 100
- Bilateral
  - + 13 14 93
- Arterial narrowing
  - + 14 15 93
- Leakage on late-phase fluorescein angiogram
  - + 6 11 55
- Perivascular sheathing
  - + 4 15 27
- Retinal hemorrhage (discrete)
  - - 2 15 13
- Inflammatory reaction
  - - 0 15 0

### Further pathological findings

- Erythrocyte sedimentation rate elevated (27–75 mm/hr)
  - + 7 15 47
- Skin rash
  - + 5# 15 33
- Drug-induced
  - - 3 5 60
- Mild eosinophilia (11–19%)
  - - 3 15 20
- Antinuclear antibody (maximum titer 1:40, 1:160, 1:320)
  - - 3 15 20
- Anti-ssDNA antibodies mildly elevated
  - - 1 15 7
- Decrease/increase of complement (C3, C4)
  - - 3 11 27

All cases are female. Cases 1 and 2 had all examinations except brain biopsies. Total cases 1-7 include three patients described in abstract form and present cases.

*Two cases with positive Hoffman’s sign, Babinski’s sign flexor.
†Vestibular and supravestibular dysfunction not differentiated.
‡Spring of 1989.
§One case with “healed angitis.”
¶Patchy skin rash under treatment with dextran 40 (April 1989).
#In five biopsies 1, 2, 4, 6 no evidence for vasculitis.
low-normal (234 nmol/l). Despite clinical improvement, the patient could not return to her job.

During a follow-up of 34 months, findings of immunological examinations (including enzyme-linked immunoassays and immunoblotting experiments for autoantibodies in serum and CSF against human brain tissue) and other biological investigations (including repeated serological tests, an adrenal function study, very long chain fatty acids, and mitochondrial deoxyribonucleic acids) were normal. In March 1991, control perimetry and nerve fiber layer examinations disclosed a new retinal defect in her left eye that had been unrecognized by the patient.

Case 2

In the summer of 1978 a 20-year-old woman developed intermittent numbness of her left arm and the left side of her face. In October 1978 she had an episode of slurred speech. She previously had been well except for chronic migraine headaches. She used oral contraceptives for a few months in 1974, 1977, and 1978 and ergotamine tartrate and dihydroergotamine during migraine headaches. In the summer of 1978 she took racemic dl-fenfluramine (60 mg/day) for 2 months.

In November 1978 she was admitted to the hospital because of blurring of vision in her left eye. General physical and neurological examinations were normal. Apart from difficulties in remembering her medical history, her intellectual faculties were unremarkable. Funduscopy showed diffuse arterial narrowing and edematous areas in the inferior parts of the left fundus without perivascular infiltrates. Fluorescein angiography showed occlusions of both the inferior temporal and inferior nasal arterioles with vascular leakage during the late phase. Results of blood work (including cultures and extensive immunologic, serological, and coagulation tests) were normal except for a mild eosinophilia (9.5%, 600/mm³) and an erythrocyte sedimentation rate of 28 mm/hr. An ECG, chest roentgenograms, and stool examinations were normal.

Despite transfusions of dextran 40 and oral pentoxifylline (600 mg/day), a further branch arteriolar occlusion in her right eye occurred. Cerebral panangiography disclosed an occlusion of a small ascending branch of the right middle cerebral artery. Angiograms of the aortic arch and the pulmonary circulation were normal as were an echocardiogram and a brain CT. Biopsy specimens of the temporal artery and rectal mucosa were normal (no vasculitis, no amyloid). The patient was discharged with an oral anticoagulant (phenprocoumon), dipyridamole (150 mg/day), and acetylsalicylate (1,000 mg/day).

In January 1980, the patient experienced intermittent paresthesias of her arms and the left side of her face. One week later, new retinal arteriolar occlusions in her right eye occurred. In mid-February 1980, while she was still taking phenprocoumon, dipyridamole, and acetylsalicylate, acute vertigo and a severe neurosensory hearing loss in her left ear occurred. Brain stem auditory evoked potentials were normal. At admission to the hospital hyperreflexia, left-sided hemihypesthesia, and a horizontal nystagmus to the right were noted. She was oriented, but her memory was impaired and her statements were sometimes inconsistent. Oral anticoagulants were stopped. Acetylsalicylate was maintained, and prednisone was given for 10 days. Cerebral panangiography revealed no new lesions; the occlusion of the small ascending branch of the right middle cerebral artery showed partial recanalization.

On February 5, 1981, new retinal arteriolar occlusions in both eyes and intermittent numbness of all four extremities occurred. A brain CT scan and coagulation studies were normal. Acetylsalicylate (1,000 mg/day) was maintained (later reduced to 100 mg/day). In 1981 the patient had to give up her job as a decorator.

In March and December 1990, coagulation studies (including ACA) were normal. A T₂-weighted MRI of the brain done in April 1991 showed multiple focal hyperintensities (no gadolinium enhancement), mainly in the basal ganglia region. During the last 10½ years her defective status has remained stable.

Discussion

To our knowledge, so far 16 young women (aged 18–40 years) have been reported to suffer from the same distinct clinical syndrome uniformly involving the brain, inner ear, and retina.¹⁻⁸ Our two patients had neurological and neuropsychological deficits (Table 1) and multifocal small hyperintensities on MRI of the brain (Figure 1). Furthermore, findings of CSF examinations and EEG in case 1 and cerebral angiography in case 2 were pathological. Both patients had a neurosensory hearing loss in the low frequency range and multiple branch retinal arteriolar occlusions with vascular leakage (Figure 2).

In three fourths of patients the beginning of the disease is abrupt, with severe neurological and/or psychiatric symptoms that are often accompanied by a hearing or vision loss. In one fourth, the first attack is preceded by several months of slowly progressive personality and mental changes. The initial symptoms generally improve either spontaneously or with immunosuppression. Each patient (n=15 [three cases not included]) suffered one to six symptomatic attacks (more than one organ system involved within 1 month considered one attack) with a mean interval of 4 (range 1–14) months. About half of the attacks involving the ear and eye are not recognized by the patient. In case 2, with a follow-up of 13 years, attacks occurred during only the first 2½ years. In most patients the disease begins with an active period (mean duration 12 months, range 1–60 months) of recurrent attacks and ends with a stable defective status of mild to moderate dementia, gait difficulties, hyperreflexia, and auditory and visual impairment. Disabling immobility, severe dementia, deafness, and blindness is rare.

Brain involvement can be demonstrated by T₂-weighted MRI with multifocal small hyperintensities in the white and gray matter of the cerebrum and cerebellum (with gadolinium enhancement during attacks), by CSF examination revealing an elevated protein content and mild pleocytosis, by EEG with diffuse slowing, by brain biopsies showing small infarcts, and occasionally by cerebral angiography demonstrating stenosed or occluded small vessels (as in the first published case¹ and our case 2). Eye involvement is demonstrated by retinal arteriolar occlusions on funduscopy or fluorescein angiography and allows the identification of microinfarcts as...
the underlying disease process. Inner ear involvement is demonstrated by a neurosensory hearing loss on pure-tone audiometry (typically of low frequencies) or by decreased vestibular responses. To indicate the patho-anatomical substrate of the disease as well as its target organs, we propose to call it the SICRET (small infarctions of cochlear, retinal, and encephalic tissue) syndrome. The severity of organ involvement may vary from patient to patient. Moreover, young women with only two organ systems involved were reported.9,10

In previous reports, systemic lupus erythematosus or a coagulopathy had been suggested as the etiology of this syndrome. Based on our immunologic and coagulation studies and the ineffectiveness of combined anticoagulant/antiplatelet treatment, we cannot support these hypotheses. Our patients were on fenfluramine before onset of the disease. This drug can cause degeneration of serotoninergic neurons and a transient decrease in dopamine turnover in rat brain.11 We found analogous changes in CSF levels of HIAA and HVA in case 1. However, it remains to be elucidated by further investigations whether these findings are causally related to the disease process.

References
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