Title: New findings of vestibular function with superficial siderosis of the central nervous system

Authors:
Toru Miwa, MD¹, Ryosei Minoda, MD, PhD¹, Hidetake Matsuyoshi, MD, PhD²

Affiliation:
¹Department of Otolaryngology and Head and Neck Surgery, Graduate of School of Medicine, Kumamoto University
²Matsubase Clinic

Reprints requested: 30
Reprint requests: Toru Miwa
Department of Otolaryngology and Head and Neck Surgery, Kumamoto University
1-1-1 Honjo, Kumamoto City, Kumamoto 860-0811, Japan
Tel: 096-373-5255 Fax: 096-373-5256
E-mail: 093r5150@st.kumamoto-u.ac.jp

Study funding: nothing

Search terms: hemosiderin, superficial sidrosis, vertigo, vestibular function, Clinical neurology examination
DISCLOSURE
Conflict of interest: The authors have declared that no conflict of interest exists.
Dr. Minoda - Study concept and design, supervision
Dr. Matsuyoshi - acquisition of data
Abstract

Background
Superficial siderosis (SS) is a condition caused by repeated or continuous bleeding into the subarachnoid space that results in iron from hemoglobin (hemosiderin) being deposited on the surface of the brain. Clinically, the condition is characterized by sensorineural deafness, dysequilibrium, and pyramidal signs. Lesions responsible for sensorineural deafness and impaired balance are primarily on the auditory (8th) nerve. Deposition of hemosiderin in the inner ear and subsequent fibrosis also causes thickening of the dura mater. As a result, blood flow of vessels supplying the inner ear decreases, possibly leading to an inner ear disorder.

Methods
Over the past 9 years in our Department, 5 were definitively diagnosed with SS by MRI. Balance testing consisted of dynamic balance testing and static balance testing. Nystagmus was examined for using an infrared camera. Electronystagmography (ENG) was used to perform an eye-tracking test (ETT), optokinetic nystagmus (OKN) test, and caloric test. In addition, the vestibular evoked myogenic potential (VEMP) was measured.

Results
Testing results revealed that all of the patients were found to have central nervous damage as well as peripheral vestibular damage. In addition, VEMP responses were present in patients who had SS for a short period but tended to be diminished or absent in patients who had the condition for a longer period.

Conclusions
These findings suggest that impaired balance due to SS must be the result of both types of damage, and functioning of the saccule-inferior vestibular nerve had been maintained before the condition progressed.
Introduction

Superficial siderosis (SS) of the central nervous system is a condition caused by repeated or continued bleeding into the subarachnoid space that results in iron from hemoglobin (hemosiderin) being deposited on the surface of the brain. Clinically, the condition is characterized by sensorineural deafness, dysequilibrium, and pyramidal signs. Lesions responsible for sensorineural deafness and impaired balance are primarily on the auditory (8th) nerve. Deposition of hemosiderin in the inner ear and subsequent fibrosis also causes thickening of the dura mater. As a result, blood flow of vessels supplying the inner ear decreases, possibly leading to an inner ear disorder. [1].

Over the past 9 years, 483 patients have been seen by this Department for impaired balance or hearing loss and undergone balance testing. Of these, 5 were definitively diagnosed with SS by MRI, so these cases are reported here along with a discussion of the literature.
Subjects and methods
Over the past 9 years, 483 patients have undergone balance testing by this Department. Of these, 5 were diagnosed with SS by MRI. Patient ages ranged from 53 to 79 years (mean: 64.5±12.6 years), and patients included 3 males and 2 females. Balance testing consisted of dynamic balance testing via a walking test and stepping test and static balance testing via Mann’s test and stabilometry (eyes open and eyes closed). Gaze nystagmus, spontaneous nystagmus, and positional and positioning nystagmus were tested for using an infrared camera. Electronystagmography (ENG) was used to perform an eye-tracking test (ETT), optokinetic nystagmus (OKN) test, and caloric test. During the caloric test, stimulation was provided by irrigation with 5 ml cold water (20 degrees celsius) for 20 sec. The maximum slow-phase velocity was measured based on ENG recordings. In addition, a vestibular evoked myogenic potential (VEMP) test was performed. The VEMP test featured 105-dB nHL clicks 0.1 ms in duration with a stimulation frequency of 5 Hz and analysis time of 50 ms; responses to 200 stimuli were averaged and a band-pass filter of 20–2000 Hz was used. The patient’s neck was rotated during testing. Hearing tests consisted of pure-tone audiometry, speech audiometry, and a distortion product otoacoustic emission (DPOAE) test.

Standard protocol approvals and patient consent
All patients provided written informed consent and the study was approved by the Kumamoto University Institutional Review Board.
Cases

Patient 1: 53-year-old female
Chief complaints: Headaches, faintness, hearing loss, tinnitus
History of the present illness: The patient was seen by this Department because of headaches, faintness, hearing loss in both ears, and tinnitus in both ears that had started several months prior.
Previous history: Unremarkable
Condition upon initial examination: tympanic membrane findings were normal. Neurologic findings were unremarkable.
Hearing test results: Pure-tone audiometry revealed mild sensorineural hearing loss in both ears (Fig. 1a). Speech audiometry and the DPOAE test were not performed.
Results of balance testing: Mann’s test and stabilometry revealed swaying when the eyes were open. The patient fell during the walking test and stepping test. During testing for nystagmus, tests for spontaneous nystagmus and positional nystagmus revealed mixed horizontal and rotatory nystagmus to the right (Fig. 1b). ETT results were normal, but OKN was not readily induced on the left. Caloric test results revealed canal paresis (CP) on the right and diminished responses on the left. VEMP responses were normal in both ears (Fig. 1c).
MRI findings: T2*-weighted images revealed hemosiderosis in the brain stem, on the surface of the cerebellum, on surface of the lateral (Sylvian) fissure and longitudinal cerebral fissure and the base of the brain, and on the 7th and 8th nerves (Fig. 1d).
Cause of hemorrhage: Unknown
Lesions responsible for impaired balance: CNS+ superior vestibular nerve

Patient 2: 55-year-old male
Chief complaint: hearing loss in both ears
History of the present illness: Bleeding was due to a cavernous hemangioma of the right ventricle; the cavernous hemangioma in the right ventricle was removed. Several weeks later, the patient had reduced hearing in both ears and was seen by this Department.
Previous history: symptomatic epilepsy, subarachnoid hemorrhage
Condition upon initial examination: Tympanic membrane findings were normal. Neurologic findings were unremarkable.
Hearing test results: Pure-tone audiometry revealed mild sloping sensorineural hearing loss on the right. On the left, reverse-cookie-bite sensorineural hearing loss was noted primarily at 1000 Hz (Fig. 2a). Speech audiometry revealed an elevated speech reception threshold in the left ear and diminished speech discrimination was noted. DPOAE responses were diminished in both ears.
Results of balance testing: In Mann's test and stabilometry, Romberg’s sign was present. Walking test results were normal; the stepping test revealed rotation of 90 degrees or more. The positional
nystagmus test revealed pendular nystagmus (Fig. 2b). The ETT revealed saccadic pursuit for both
eyes, and OKN was not readily induced in either eye. Caloric test results were normal on the left
but responses were diminished on the right. A visual suppression test also revealed diminished
responses. VEMP responses were present in both ears (Fig. 2c).
Imaging study findings: T2-weighted images revealed hemosiderosis in the cerebellum, around the
medulla oblongata, and in the right temporal lobe (Fig. 2d).
CSF findings: Bloody CSF
Cause of hemorrhage: subarachnoid hemorrhage
Lesions responsible for impaired balance: CNS+ superior vestibular nerve

Patient 3: 71-year-old female
Chief complaints: hearing loss, faintness
History of the present illness: The patient noticed hearing loss on the left a year prior and faintness 8
months prior but did not seek treatment. Two months prior, the patient developed hearing loss on
the right and was seen by this Department.
Previous history: Unremarkable
Condition upon initial examination: Tympanic membrane findings indicated a somewhat cloudy
membrane in both ears. Attic retraction was noted on the left. Neurologic findings were not
remarkable.
Hearing test results: Pure-tone audiometry revealed moderate sensorineural hearing loss on the right
and moderate mixed conductive-sensorineural hearing loss on the left (Fig. 3a). Speech audiometry
revealed an elevated speech reception threshold in both ears and diminished speech discrimination
was noted in the left ear.
Results of balance testing: Mann’s test and stabilometry revealed swaying when the eyes were open
(Fig. 3b). The patient fell during both the walking test and stepping test. During nystagmus
testing, the positional nystagmus test revealed horizontal nystagmus to the right (Fig. 3c). ETT
results revealed somewhat saccadic pursuit in both directions. OKN was not readily induced in
either eye. Caloric responses were absent in both ears and VEMP responses were absent in both
ears (Fig. 3d).
Imaging study findings: T2*-weighted images revealed hemosiderosis in the brain stem and surface
of the cerebellum, lateral (Sylvian) fissure, and longitudinal cerebral fissure (Fig. 3e).
Cause of hemorrhage: Unknown
Lesions responsible for impaired balance: CNS+ superior and inferior vestibular nerves

Patient 4: 73-year-old male
Chief complaints: hearing loss on the left, vertigo
History of the present illness: The patient had hearing loss on the left and tinnitus 2 to 3 years prior that gradually worsened. The patient also developed vertigo and was seen by this Department.

Previous history: At age 33, surgery for a tumor in the right orbit and radiation therapy; at age 50, removal of a cyst in the right temporal lobe

Condition upon initial examination: Tympanic membrane findings were normal. In terms of neurologic findings, a finger-to-nose test revealed a lack of coordination on both sides.

Hearing test results: Pure-tone audiometry revealed moderate sensorineural hearing loss on the right and severe sensorineural hearing loss on the left (Fig. 4a). Speech audiometry revealed an elevated speech reception threshold for both ears and diminished speech discrimination was noted for both ears. DPOAE responses were diminished in both ears.

Results of balance testing: Mann’s test and stabilometry revealed swaying when the eyes were open (Fig. 4b), but walking test and stepping test results revealed no abnormalities. During nystagmus testing, the positional nystagmus test revealed horizontal nystagmus to the left (Fig. 4c). ETT revealed saccadic pursuit for both eyes. OKN was not readily induced in either eye. The caloric test indicated CP in both ears. VEMP responses were absent in both ears (Fig. 4d).

Imaging study findings: T2* -weighted images revealed hemosiderosis in the right frontal lobe and temporal lobe and in the margins of the basis ganglia (Fig. 4e).

Cause of hemorrhage: complications following brain surgery

Lesions responsible for impaired balance: CNS+ superior and inferior vestibular nerves

Patient 5: 79-year-old male

Chief complaint: Hearing loss in both ears

History of the present illness: Hearing loss gradually worsened starting 17 years prior. The patient requested implantation of a cochlear implant and was seen by this Department.

Previous history: hypertension, mitral valve replacement 5 years prior

Condition upon initial examination: Tympanic membrane findings were normal. In terms of neurologic findings, a finger-to-nose test revealed a lack of coordination on the left.

Hearing test results: Deafness in both ears (Fig. 5a). Speech audiometry was not possible. DPOAE responses were absent in both ears.

Results of balance testing: Mann’s test and stabilometry results were normal (Fig. 5b). Walking test results were also normal, but the patient fell during the stepping test. During nystagmus testing, the positional nystagmus test revealed alternating (up-beating) nystagmus (Fig. 5c). ETT revealed saccadic pursuit for both eyes. OKN was not readily induced in either eye. The caloric test indicated CP in both ears. VEMP responses were diminished on the left (Fig. 5d).

Imaging study findings: T2-weighted images revealed hemosiderosis on the surface of the cerebellum and around the brain stem (Fig. 5e).
Cause of hemorrhage: Unknown (microbleeds due to chronic hypertension)
Lesions responsible for impaired balance: CNS+ superior and inferior vestibular nerves
Discussion

SS is a condition caused by repeated or continued bleeding into the subarachnoid space that results in iron from hemoglobin (hemosiderin) being deposited on the surface of the brain. Clinically, the condition is characterized by sensorineural deafness, impaired balance, and pyramidal signs. The condition was reported by Hamill in 1908 [2], and autopsies of 2 affected patients were reported in 1940 [3]. Later, the widespread use of MRI allowed the condition to be diagnosed prenatally. As of today, 270 cases [4] have been reported in the literature.

Hemosiderosis is thought to develop specifically in the central nervous system in contact the cerebrospinal fluid (the subarachnoid space) but not in the peripheral nervous system [5, 6]. Thus, impaired balance was thought to be caused by hemosiderosis of the central nervous system and subsequent tissue injury [3]. Nevertheless, recent results of balance testing and pathology findings indicate differently. Specifically, caloric tests revealed CP [7-13] and temporal bone pathology revealed atrophy of the superior & inferior vestibular nerves and loss of hair cells [14]. Thus, impaired balance due to SS is now reportedly due to central nervous damage and peripheral vestibular damage [1, 14-16]. Peripheral vestibular injury can be the result of deposition of hemosiderin in the inner ear and subsequent fibrosis that cause thickening of the dura mater. Blood flow of vessels supplying the inner ear decreases, possibly leading to an inner ear disorder [1].

The current study involved 5 patients who were seen by this Department for impaired balance or hearing loss were definitively diagnosed with SS by MRI. These patients underwent balancing testing that included a VEMP test. All of the patients were found to have evidence of central nervous damage and peripheral vestibular damage; this finding is the same as that in the latest reports. In addition, the balance testing of the current patients included a VEMP test, which previous patients with SS had seldom undergone, and the saccule-inferior vestibular nerve was assessed. Only 31 patients are reported to have undergone otologic evaluation of sensorineural deafness and impaired balance due to SS [4]. Of these, only 16 underwent balance testing [17]. Moreover, only 1 patient underwent a VEMP test [13]. Broadly, results of the VEMP test for the 5 patients seen by this Department indicated that VEMP responses were normal for patients who had SS for a short period but VEMP responses tended to be diminished or absent for patients who have had the condition for a longer period (Fig. 6). That is, functioning of the saccule-inferior vestibular nerve was maintained in patients who had the condition for a short period. In the case reported by Ushio et al., the patient had had the condition for a long period of 21 years; a caloric test revealed CP in both ears and VEMP responses were absent in both ears [13]. Similarly, the current results indicated that vestibular function facilitated by the superior vestibular nerve was diminished or absent in all of the patients (Fig. 6). Vestibular damage to the superior vestibular nerve tended to precede vestibular damage to the inferior vestibular nerve. Anatomically, the superior vestibular nerve is longer and travels through smaller osseous neural canals [18]. Thus, more surface area of
the nerve is in contact with cerebrospinal fluid, so hemosiderin is readily deposited and constriction and impaired blood flow readily develop. Thus, the superior vestibular nerve is relatively susceptible to damage with the inferior vestibular nerve is not. However, MRI findings revealed hemosiderosis of the eighth nerve in only 1 patient (Fig. 6). Peripheral vestibular injury is likely caused by constriction and impaired blood flow than by tissue injury due to deposition of hemosiderin. This corroborates the report by Fukiyama et al. indicating that peripheral vestibular injury due to SS was caused by impaired blood flow in the inner ear.

Treatment of SS involves identifying the cause of bleeding and then treating the organic underlying cause when it is apparent. When it is not apparent, a chelating agent is administered to deplete iron or a hemostatic agent is administered. However, such treatment is inadequate and effective therapies have yet to be established [7, 19]. In Patients 1-5, the cause of bleeding was apparent in Patients 2 and 4 (Patient 2: subarachnoid hemorrhage; Patient 4: brain tumor, complications following brain surgery). In these patients, the underlying cause was already being treated when the patients were initially examined by this Department. Causes of bleeding due to SS are reported to include cerebral aneurysm, arteriovenous malformation, vascular lesions such as angioma, neoplastic lesions of the brain and spine, and complications following brain surgery [19-28]. About half, however, are idiopathic [7]. Another cause of bleeding can be microbleeds due to chronic hypertension. In patients with hypertension, microbleeds into the subarachnoid space continue due to the fragility of vessels in the meninges [29]. The cause of bleeding in Patient 5 could have been microbleeds due to chronic hypertension. None of the patients seen by this Department were administered a hemostatic agent or chelating agent. A hemostatic agent or chelating agent should probably be administered to patients with bleeding that has not been curbed to halt the exacerbation of sensorineural deafness and impaired balance.

The prognosis for SS is relatively good, with some patients surviving 20 to 30 years after developing the condition [7, 21, 30]. Sensorineural deafness often progresses and QOL is markedly diminished. Recently, the increasing implantation of cochlear implants has been accompanied by an increase in the number of patients receiving a cochlear implant to treat severe sensorineural hearing loss due to SS [8, 9, 31-37]. Given the fact that impaired balance is due to central nervous damage and peripheral vestibular damage as reported earlier, acquiring or achieving balance via the vestibuloocular reflex will prove difficult. There is no compensatory mechanism and symptoms will persist, often diminishing QOL. The course of the current patients could not be followed, so diminishing of vestibular function could not be ascertained. However, periodic balance testing could probably facilitate observation of the diminishing of vestibular function.

This report revealed that the lesions responsible for impaired balance due to SS are in the central nervous system and the peripheral vestibular system. Vestibular function facilitated by the saccule-inferior vestibular nerve readily diminishes the longer a patient has the condition.
Nevertheless, the pathology of SS remains rather unclear and effective therapies have yet to be established. This point must be examined in the future by assembling additional cases.
References


**Figure legend**

Figure 1: Patient 1

b. Nystagmus tests: spontaneous nystagmus and positional nystagmus revealed mixed horizontal and rotatory nystagmus to the right.

c. VEMP: bilaterally normal

d. MRI: T2*-weighted images revealed hemosiderosis in the brain stem, on the surface of the cerebellum, on surface of the lateral (Sylvian) fissure and longitudinal cerebral fissure and the base of the brain, and on the seventh and eighth nerves (arrow).

Figure 2: Patient 2

b. Nystagmus tests: positional nystagmus test revealed pendular nystagmus

c. VEMP: bilaterally normal

d. MRI: T2-weighted images revealed hemosiderosis in the cerebellum, around the medulla oblongata, and in the right temporal lobe (arrow).

Figure 3: Patient 3
a. Pure-tone audiometry: moderate sensorineural hearing loss on the right and moderate mixed conductive-sensorineural hearing loss on the left

b. Stabilometry: swaying when the eyes were open

c. Nystagmus test: positional nystagmus test revealed horizontal nystagmus to the right

d. VEMP: bilaterally absent

e. MRI: T2*-weighted images revealed hemosiderosis in the brain stem and surface of the cerebellum, lateral (Sylvian) fissure, and longitudinal cerebral fissure (arrow).

Figure 4: Patient 4
a. Pure-tone audiometry: moderate sensorineural hearing loss on the right and severe sensorineural hearing loss on the left.

b. Stabilometry: swaying when the eyes were open

c. Nystagmus test: the positional nystagmus test revealed horizontal nystagmus to the left

d. VEMP: bilaterally absent

e. MRI: T2*-weighted images revealed hemosiderosis in the right frontal lobe and temporal lobe and in the margins of the basis ganglia (arrow),
Figure 5: Patient 5
a. Pure-tone audiometry: Bilaterally Deafness
b. Stabilometry: normal
c. Nystagmus test: the positional nystagmus test revealed alternating (up-beating) nystagmus.
d. VEMP: diminished on the left
e. MRI: T2-weighted images revealed hemosiderosis on the surface of the cerebellum and around the brain stem (arrow).
Fig. 2

a

b

gaze  ungaze


c

d

Figure 2
Fig. 3

(a) Graph showing data with frequency on the x-axis and dB on the y-axis.

(b) Two scatter plots with data points.

(c) Diagrams labeled 'gaze' and 'ungaze' with patterns.

(d) Graphs with two waves and numerical labels.

(e) Magnetic Resonance Imaging (MRI) scan with arrows indicating specific areas.
Fig. 4

(a) Graph showing dB values against frequency (Hz) from 125 to 8000 Hz.

(b) Graphs illustrating gaze and ungaze conditions.

(c) Diagrams depicting gaze and ungaze states with arrows indicating movement.

(d) Oscilloscope trace of signal output.

(e) MRI image indicating brain structures with arrows pointing to specific areas.
Fig. 5

(a) Graph with various markers and data points.
(b) Two scatter plots showing data distribution.
(c) Diagrams illustrating gaze and un-gaze with symbols.
(d) Two waveforms with labels.
(e) MRI scan with arrows indicating specific regions.