

Saccade testing in the diagnosis and treatment of type 3 Gaucher disease

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Gaucher disease (GD) is an autosomal recessive lysosomal disorder caused by a deficiency of glucocerebrosidase. Partial deficiency produces type 1 GD (GD1), while severe deficiency yields the two less common types of neuronopathic GD (GD2 and GD3). GD3 can develop at birth up until age 14 years and is characterized by splenomegaly and fever, growth retardation, and bone changes with thinning of the cortices. Intellectual deterioration and neurologic manifestations, like seizures, occur later in the course of the disease. Oculomotor signs, such as squint, difficulty in generating horizontal saccades (saccadic initiation failure, SIF), and saccadic slowing, are present and may precede the emergence of overt neurologic signs by many years.¹ Enzyme replacement therapy (ERT) is effective in most GD1 while its efficacy in neuronopathic GD is less clear. It may relieve the systemic component of GD2, but does not reverse neurologic symptoms.² In GD3, reports are inconsistent. Some patients show partial neurologic remission and others show progression.^{3,4} Data about eye movement modifications in GD3 both during its natural history and ERT are not available. In order to study the possible effect of ERT on neurologic symptoms, we annually recorded the saccadic eye movements in a boy with GD3, from ages 6 to 11 years.

Methods. A 5-year-old boy presented with splenomegaly and a slight speech lag. After the diagnosis of GD, ERT was begun (Imiglucerase, 30 U/kg every 2 weeks). The patient's genotype was P159T/recombinant allele and the initial enzyme activity was 2.5 nmol/mg/hour. One year later, he showed no reduction of splenomegaly and alterations at the first saccadic eye movement recording, so the dose of Imiglucerase was doubled. Splenomegaly reduced to half after 1 year and then remained unchanged. At age 11 years, neurologic examination and EEG were normal. Saccadic movements of both eyes were recorded by infrared limbus tracking technique, with the subject tracking a randomly moving horizontal target in a visual range of ± 15 deg with amplitudes of 5, 10, 15, and 20 deg. For each identified saccade, the amplitude (A), duration (D), latency, and peak velocity (Vp) were calculated. A/D and A/Vp relationships were evaluated and best-fitted. The fitting curves $D = m \cdot A + q$ (for the A/D) and $Vp = 1/(\alpha + \beta/A)$ (for the A/Vp) were used. The K (mean velocity/peak velocity ratio) and skewness (saccadic rise time/duration ratio) measures were also evaluated.^{5,6}

Results and discussion. The first recording showed a large number of blinks and some tracts of SIF, both typical of neuronopathic GD. We found the largest latencies (257 ± 55 msec) and the lowest peak velocities, with a saturation value ($1/\alpha$) of 641 deg/second, among all registrations. The control group consisted of 10 healthy age-matched children. The intersubject average values were $1/\alpha = 1166 \pm 373$ deg/second, $1/\beta$ (the best-fit curve slope for low amplitudes) = 60.0 ± 18.3 s⁻¹, $m = 1.81 \pm 0.52$ msec/deg, $q = 32 \pm 5.7$ msec, skewness = 0.08 ± 0.08 , $K = 0.51 \pm 0.03$, latency = 196 ± 15 msec. The $1/\alpha$ values and latencies were ($p < 0.01$ at Student t test) different from those measured in the first recording.

Following the ERT dose increment, an improvement of saccadic characteristics was detected in the two successive examinations, and subsequently stabilized. SIF was no longer, blinks were rare, latencies were shorter (202 ± 52 msec), and peak velocities were higher than in the first examination. All values were in the normal range. In normal subjects the skewness linearly decreases and K linearly increases as the amplitude increases, while in some patients with GD these linear relations are obscured in one or in both eyes as a result of increase of variability.⁶ In our case (figure, A and C) data spreading was wide in the first examination, while it decreased after 2 years of therapy (figure, B and D). Therefore, in this GD3 patient, a high ERT dose at the first neurologic symptoms resolved the brainstem manifestations, but only after 2 years of therapy. The limited success of ERT in reversing the neurologic symptoms of GD is not due to the lack of efficacy of imiglucerase in CNS neurons⁷ but reflects the poor permeability of the blood-brain barrier or the rapid CNS turnover of this enzyme.²

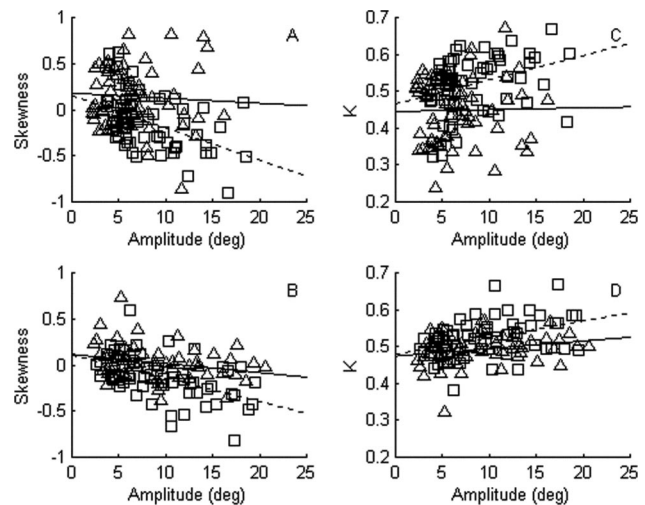


Figure. Skewness vs amplitude (A, B) and K vs amplitude (C, D) relationships in the first (A, C) and third (B, D) tests. Skewness: right eye: -0.12 ± 0.29 (A), -0.13 ± 0.24 (B); left eye: 0.14 ± 0.37 (A), 0.026 ± 0.19 (B). K: right eye: 0.52 ± 0.075 (C), 0.52 ± 0.052 (D); left eye: 0.45 ± 0.086 (C), 0.49 ± 0.041 (D). In the skewness/amplitude relation, a reduction of the data spreading in the third test with respect to the first one and a decrease of the slope (mean and SD values) of the left eye linear regression (solid line) are present. Square: right eye; triangle: left eye. Dashed line: linear best fit of the right eye data; solid line: linear best fit of the left eye data.

Therefore, continuous replacement of glucocerebrosidase in the CNS is necessary for the treatment of neuronopathic GD. Further studies are necessary to evaluate higher ERT dosages and new methods of administration to bypass the brain barrier.

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Dementia due to neurosyphilis with persistently negative CSF VDRL

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A 44-year-old right-handed homosexual man was referred for gradual deterioration of skills as a chef, impairment of memory, and decreased fluency and comprehension of speech. He had prominent personality change from an easygoing nature to irritability and anxiety. Over a year, his mental abilities deteriorated such that he was unable to drive a car, maintain a job, or live independently. He had no prior neurologic, psychiatric, or systemic illness.

Episodes of agitation, confusion, and body tremors appeared 1.5 years after onset. Evaluation by a neurologist at that time at another hospital revealed disorientation, disinhibition, poor attention and recall, tremors during handwriting, and motor impersistence. Mini-Mental State Examination score was 23 out of 30. There was diffuse cerebral atrophy on MRI (figure, A), and the EEG was normal. CSF had protein of 97 mg/dL, 1 WBC/mm³, and many oligoclonal bands. CSF Venereal Disease Research Laboratory test (VDRL), CSF 14-3-3 level, serum HIV and Lyme antibody, toxicology screen, thyroid and liver functions, vitamin B12, erythrocyte sedimentation rate, antinuclear antibody, and rheumatoid factor were unremarkable. Serum RPR was not tested.

Reevaluation for further deterioration 6 months later revealed childish behavior, emotional lability and irritability, mildly dysfluent speech, and dysgraphia. Pupils were normal in size, shape, and reaction to light and near vision. There was an inconstant perioral tremor along with postural and action tremors in both arms and generalized hyperreflexia without Babinski signs. Sensation, coordination, and gait were normal. Neuropsychological testing showed marked deficits in attention, immediate and delayed memory, and executive frontal system functions with milder impairments in visuospatial and language tasks.

MRI revealed the new finding of non-enhancing T2 and fluid attenuated inversion recovery (FLAIR) hyperintensities in the left mesial temporal lobe (figure, B). Repeat CSF examination revealed protein of 88 mg/dL and 41 WBC/mm³ (86% lymphocytes). Repeated CSF VDRL was negative. CSF cryptococcal antigen, angiotensin converting enzyme, PCR for herpes simplex virus and human herpesvirus 6, and cytology for malignant cells were negative. Serologies for HIV, Lyme, and paraneoplastic antibodies were negative. EEG revealed diffuse slowing. Serum RPR test was positive at 1:128, serum Treponema pallidum particle agglutination (TP-PA), and CSF fluorescent Treponemal antibody-absorption (FTA-Abs) were positive. A left temporal lobe biopsy was done because of deteriorating agitation and confusion before the syphilis serology results returned. It showed elongated microglia, astrogliosis, and scant plasma cells (see figure E-1 on the Neurology Web site at www.neurology.org) and was positive for Treponema pallidum by PCR assay performed by the Centers for Disease Control and Prevention Laboratory of Clinical Immunology and Molecular Medicine, Atlanta, GA. The patient was treated with IV penicillin for 14 days. Six months later, his cognitive functions had improved, but he had developed delusions of persecution and auditory hallucinations. Repeat CSF examination showed resolution of the prior abnormalities.

Discussion. Cerebral neurosyphilis manifest by dementia with slowly progressive cognitive, social, occupational, and personality dilapidation (general paresis of the insane) was well known in the pre-penicillin era. The recent increase in primary and secondary syphilis in men who have sex with men¹ necessitates continued awareness of neurosyphilis even without HIV coinfection.²

Our patient illustrates the difficulties in the laboratory confirmation of neurosyphilis. CSF VDRL is specific for neurosyphilis

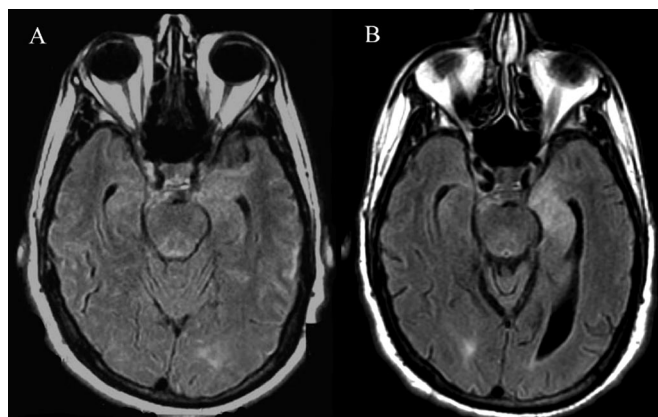


Figure. MRI with the fluid attenuated inversion recovery sequence. (A) Six months prior to admission. (B) At the time of admission. There has been development of high intensity signal in the left mesial temporal region.

but is negative in 28 to 78% of patients.³⁻⁵ In our patient CSF VDRL was negative on two occasions, at about 1 and half years and 2 years into the clinical course. Treponeme-specific FTA-Abs in the CSF, on the other hand, is sensitive but not specific for neurosyphilis⁶ so that negative reaction is helpful in excluding the diagnosis. Lack of cellular reaction in active neurosyphilis is exceptional. The absence of CSF pleocytosis at initial examination and brisk lymphocytosis months later supports the value of repeated testing. A negative VDRL test in the CSF and the absence of pleocytosis do not obviate the need for serum RPR testing, although sensitivity of this test may decrease to as low as 70%⁷ over time in late stage neurosyphilis. Rarely, in secondary stage syphilis, serum RPR is falsely negative due to the prozone phenomenon of very high antibody titers; this can be corrected by serial dilution of the serum. Treponemal tests such as FTA-Abs are generally used as confirmatory tests when the non-treponemal tests are positive or when the clinical suspicion of syphilis is high despite a negative screening test.

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Diaphragmatic flutter after spinal cord trauma in a child

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Diaphragmatic flutter (DF) is an infrequent movement disorder characterized by bursts of rhythmic contractions of the diaphragm and other muscles innervated by cervical roots. Clinically it looks like an involuntary irregular rhythmic movement of the abdominal wall, very often associated with abdominal wall pain and dyspnea.¹ Many terms have been proposed: diaphragmatic myoclonus (convulsions, tremor, spasms, cramps, rumbles, pulsations), moving umbilicus, and belly dancer.² EMG recordings demonstrated a frequency of the contraction between 0.5 and 15 Hz, more often around 4 to 6 Hz. For a correct diagnosis, an EMG of the diaphragm and the scalene muscles should show repetitive contractions.^{3,4} Its mechanism is not fully understood. Different kinds of neurologic lesions, both central and peripheral, were related to DF.⁵ Several drugs (carbamazepine, phenytoin, chlorpromazine, benzodiazepines) can be useful.^{2,3}

Case report. A 12-year-old girl fell. Extreme flexion of her neck was immediately followed by tetraparesis, paraesthesias, and numbness. Emergency spinal radiographs and MRI showed no abnormalities. Neurologic deficits disappeared in the 10 hours following the accident. Four days later, she started having bursts of abdominal jerks, continuously in wakefulness and absent during sleep. One month later, she came to our hospital because of the persistence of the movements. Neurologic examination was normal. Repeated plain radiographs and MRI of the cervical spine were normal. Fluoroscopy of the chest and abdomen demonstrated bilateral fluttering bursts of the diaphragm predominantly with the inspiratory excursions.

A surface EMG recording was performed including several muscles (scalene, intercostals, and accelerometer in the abdominal wall in both sides) (figure). The movements of the abdominal wall originated by active contraction of diaphragm were rhythmic at a frequency of 4 to 5 Hz (see the figure, C, channel 7). They appeared predominantly in inspiration. In the scaleni EMG (see the figure, channels 1 and 4), periodic bursts of EMG activity were bilaterally noted; they were bilateral and synchronous. A 20-hour polygraphic-video-EEG study demonstrated 5 Hz rhythmic slow waves that appeared bilaterally in the inspiratory phase; the movements appeared in wakefulness, at rest, and in motion, and disappeared during sleep (see the video on the *Neurology* Web site at www.neurology.org). Carbamazepine 20 mg/Kg/day was started. Ten months later the abnormal movements were absent, and carbamazepine was progressively tapered. Eighteen months after the accident, the patient remains asymptomatic without taking any medication.

Discussion. Diaphragmatic flutter is not included in the Jankovic classification of movement disorders.⁶ There is an open debate on whether DF can be considered diaphragmatic myoclonus or if it deserves a specific name. In some articles both names are used indistinctly.^{2,5,7} Diaphragmatic myoclonus should be reserved for the movements concurring with the palatal myoclonus or tremor, secondarily to lesions in dento-rubro-olivary circuit or Mollaret's triangle. They are continuous and very often they persist during sleep. Their EMG burst rate is slower. They are not affected by external or psychic factors and they do not alter the normal movements of the patient. Propriospinal myoclonia are originated in a level of the spine and spread to other levels producing jerking in contiguous metameric levels with a typical delay between the muscles according to the proximity to the pacemaker, both in rostral and caudal direction. Spinal myoclonus is another kind of limited myoclonus being restricted to a metamer level without spreading to other areas. DF has also to be distinguished from retching, as seen in the Tourette disorder. Considering this differential diagnosis, our case can also be considered as a cervical myoclonus, but the involvement of the diaphragm, the higher rate (spinal myoclonus tend to be slower), the efficacy of carbamaz-

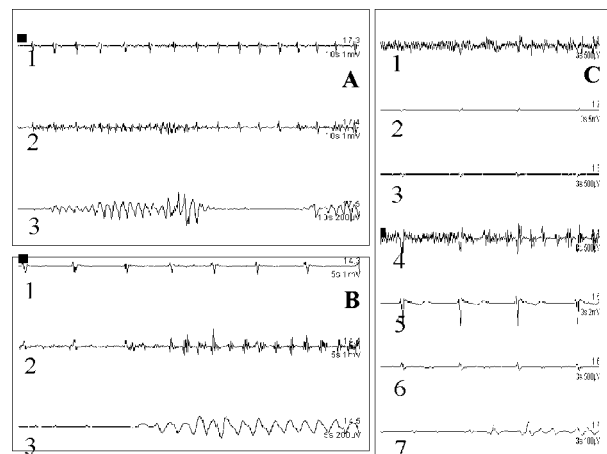


Figure. Surface EMG recording. (A and B) 1, Intercostals; 2, scalene; 3, abdominal wall (with an accelerometer). At the same time as the movements in the abdominal wall there are EMG contractions in the scalene muscle. (C) 1, Left scalene; 2, left intercostals; 3, left abdominal wall; 4, right scalene; 5, right intercostals; 6, right abdominal wall; 7, abdominal wall with accelerometer. The contractions in the scalene muscles are bilateral and synchronous (channels 1 and 4). These contractions were simultaneous to the rhythmic movements of the abdominal wall (channel 7), but no EMG activity was observed on the abdominal or intercostal muscles (channels 2, 3, 5, and 6).

epine, and the relationship with the inspiration support the distinction of DF as a peculiar entity.

Both peripheral and central causes have been advocated as related with this rare disorder. For some authors the generator is most likely central, in the rostral medulla.⁴ It is mainly an inspiratory phenomenon, and both the phrenic and the scalene have an inspiratory function. In our case, the bilaterality of the EMG activity and the relationship with the spinal trauma support the idea of a central mechanism, involving the upper part of the spinal cord, inducing the discharges of the cervical roots. Also, peripheral lesions of the roots might be implicated in our case due to the stretch to the cervical roots. The positive response to carbamazepine is important but it does not define the etiology or the mechanism.

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Cefepime- and cefixime-induced encephalopathy in a patient with normal renal function

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Cephalosporin-induced encephalopathy is well described in patients with impairment of renal function.¹ We report a case of probable recurrent cephalosporin-induced encephalopathy in a patient without renal failure.

Case report. An 85-year-old man was admitted to the intensive care unit because of sepsis syndrome and abdominal pain. He had history of hypertension, obesity, a coronary artery bypass graft, colon cancer surgically treated with remission, abdominal aneurysm surgically corrected, and deep venous thrombosis on oral anticoagulation. He experienced an acute confusional syndrome during a previous admission due to an epididymitis treated with a cephalosporin.

The admission initial workup suggested an acute urinary tract infection. His Acute Physiology and Chronic Health Evaluation (APACHE) II was 13. His serum creatinine level was 0.8 mg/dL. He started cefepime 1 g IV BID and amikacin 1 g IV per day. After 48 hours, he continued only with cefepime 2 g IV BID, as blood and urinary cultures were positive for *Escherichia coli*. Twenty hours later, he developed acute delirium, which was treated with IV haloperidol (2.5 mg) and oral olanzapine (2.5 mg) with partial success. Brain CT was normal. His neurologic condition further deteriorated; he was stuporous, pupils were symmetric and reactive to light, ocular fundus was normal; extraocular movements were full; no deficits were found in the remainder of the cranial nerves. There were no meningeal signs, and neither focal motor nor sensory deficits were present. Deep tendon reflexes and plantar responses were normal. He had no hemodynamic alteration, and temperature was normal. He was intubated. He had normal arterial blood gases, blood cell count, serum chemistry test, and ammonium level. His creatinine level was 0.8 mg/dL and his 24-hour measured creatinine clearance was 75 mL/min that day. He had repeat negative blood, urinary, and bronchial lavage cultures. He had a normal CSF examination. An EEG showed slow symmetric 4- to 7-Hz wave activity but no evidence of epileptic discharges. Because of the possibility of drug-induced encephalopathy, psychotropic drugs and cefepime were stopped, and the antibiotic was changed to piperacillin-tazobactam. One day after withdrawal of cefepime, his neurologic status markedly improved, and the patient was extubated. After 7 days of IV antibiotic treatment, the patient received cefixime 400 mg/day PO. Thirty-six hours later, his conscious state gradually deteriorated, with delirium and stupor leading again to the need for tracheal intubation. His renal function remained normal (creatinine 0.7 mg/dL). Despite exhaustive workup, no etiology other than cefixime was found to explain the encephalopathy. The antibiotic was changed, and the patient fully recovered in less than 36 hours. He completed treatment and was discharged with a normal neurologic status.

Discussion. Cefepime and cefixime are eliminated mainly by renal excretion. Previous reports of neurotoxicity associated with cephalosporins have been described in patients with renal failure or overdose.^{1,4} We have not found reports of encephalopathy induced by cefepime or cefixime in patients with normal renal function.

Our patient was under treatment with amikacin, which could potentially affect renal function. However, it was discontinued before the first episode of encephalopathy, and there were no fluctuations in renal function during the admission. Cefepime and amikacin are excreted primarily in urine by the glomerular filtration process and are poorly bound to serum proteins. There is proof of no pharmacokinetic interaction between these drugs in humans.⁵ Therefore, it is unlikely that the co-administration of these drugs generated high levels of blood cefepime. We have not measured cefepime blood concentration.

Cephalosporin treatment may induce endotoxin release, which generates cytokines liberation, such as tumor necrosis factor- α . Tumor necrosis factor- α seems to mediate septic encephalopathy.⁶ Although it may have been the mechanism of the first episode of encephalopathy, it was unlikely to be responsible for the second one, as it did not develop until the 7th day of antibiotic treatment.

Alternatively, cephalosporins may decrease γ -aminobutyric acid release from nerve terminals, increase excitatory amino acid release, and exert a competitive antagonism with γ -aminobutyric acid.⁷ The temporal association of the encephalopathy induction and resolution with the cefepime and cefixime administration and withdrawal makes the two drugs highly likely to be responsible for the encephalopathy.

In patients with renal impairment, there are reports of nonconvulsive status epilepticus and metabolic encephalopathy associated with cefepime. The EEG in these patients showed paroxysmal activity or triphasic sharp waves,^{1,4} but in our patient, no seizure activity was found.

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Hypogeusia and hearing loss in a patient with an inferior collicular infarction

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Various vascular syndromes have been described in patients with midbrain infarction.^{1,2}

The clinical picture is dominated by third-nerve palsy, conjugate or disconjugate gaze impairment, contralateral motor and sensory deficit and homolateral or contralateral limb ataxia. We

describe a patient with a pontomesencephalic tegmental infarction with hearing loss and hypogeusia as dominant features.

Case report. A 52-year-old man had dizziness and loss of taste while eating dinner. The next morning upon awakening, he developed sensory changes of the left half of his face, clumsiness of the right arm and leg, and sensation of bilateral ear wadding. At admission, neurologic examination revealed right limb ataxia, decreased pinprick and touch sensation over the left half of his face, and bilateral hypoacusia, more marked on the left side. There was a marked diminution of taste on the left side of the tongue. His taste was examined by application of 0.5 M NaCl, 10% glucose, 0.2 M acetic acid, and 0.02 M quinine. The rest of the neurologic

examination was normal. Limb ataxia and left face hypoesthesia gradually disappeared, and 10 days later only left tongue hypogeusia and hypacusia were present. Conventional vascular risk factors were absent except for a mild hypertension.

Noncontrast cranial CT was normal. Brain MRI performed 5 days later revealed a small ischemic lesion in the right tegmental portion of the upper pons and lower midbrain (figure, A through C); no abnormality was detected in other parts of the brain or spinal cord. CSF examination was normal including oligoclonal bands. Carotid, vertebral, and basilar arteries were normal at duplex ultrasonography and at MR angiography.

Transthoracic and transesophageal echocardiography failed in revealing cardiac sources of embolism. According to clinical and neuroradiologic features, a diagnosis of lacunar infarction in the territory of a deep branch of the superior cerebellar artery (SCA) was made. Standard pure-tone audiometry showed a bilateral hearing impairment for high frequencies, more evident on the left side. Brainstem auditory evoked potentials showed an increased latency of wave V and of the III to V interval on the left side. Three months later, midleft tongue hypogeusia and hypacusia were still present.

Discussion. Our patient presented a dorsal pontomesencephalic infarct with contralateral hypogeusia and hearing loss as dominant and persistent symptoms. Midbrain infarctions occur either in isolation or, more frequently, associated with cerebellar, thalamic, or occipital lesions.² In the majority of the cases, the infarctions are located in the ventral and tegmental portion of the mesencephalon and rarely involve the tectum and collicular areas. The arterial blood supply to midbrain is complex, with five arterial trunks: the medial branch of the SCA, the collicular artery, the posteromedial choroidal artery, the interpeduncular branch of the posterior cerebral artery, and the anterior choroidal artery. In our patient, the infarction involved the laterotegmental portion of the upper pons and the inferior colliculus in the lower midbrain, supplied by the medial branch of the SCA. Notably, SCA infarctions more commonly involve the rostral cerebellum alone² and usually spare the brainstem territory supplied by the deep branches arising early from the patent trunk.

Regarding the anatomicoclinical correlation in our patient, homolateral limb ataxia results from involvement of the upper cerebellar peduncle carrying cerebellar–thalamic fibers, whereas facial contralateral sensory loss results from involvement of the crossed trigeminal lemniscus, running in the dorsolateral mesencephalon (see figure, D).

Hypogeusia and hearing loss were the dominant and persistent symptoms. In stroke patients, hearing loss is uncommon owing to the organization of the central auditory pathways, which consist of more nuclei intercalated and extensive interconnections among them.³ Virtually all ascending auditory fibers synapse in the inferior colliculus both ipsilaterally and contralaterally. The infarction involves the lateral lemniscus and the inferior colliculus (see figure, D). The predominance of hypacusia on the contralateral side suggests that acoustic fibers are mostly crossed at the level of the inferior colliculus.

Hypogeusia has been described mainly in infarcts involving the thalamus and the posterior part of the corona radiata, which conveys gustatory pathways from the thalamus to the insular cortex. However, the localization of the secondary gustatory pathway is still uncertain, in particular regarding the level of decussation in the brainstem.⁴ Few cases of ipsilateral hemiageusia due to ischemic lesion of the tegmental portion of both the pons and the mesencephalon have been described, suggesting that the gustatory fibers cross up the level of the upper pons or lower midbrain.^{4,6} More recently, a patient with ipsilateral hemiageusia and an infarction of the upper dorsal pons has been described,⁵ and some authors described a case of bilateral gustatory loss in a patient with unilateral tegmental pontine demyelinated lesion.⁷ In our patient, the hemiageusia was contralateral to the infarction, suggesting the involvement of the crossed fibers at the upper pontine level.

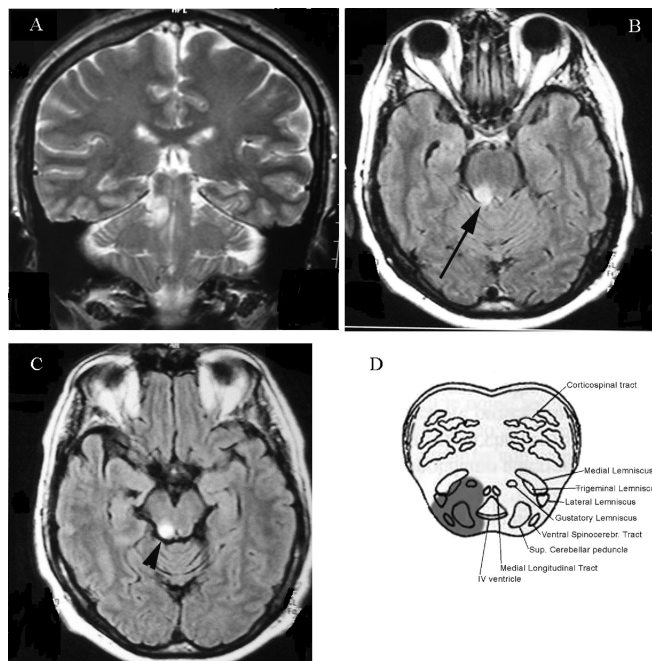


Figure. (A) Brain MRI (T2 excitation, coronal scan). The ischemic lesion involves the lateral portion of the upper brainstem, rostrally to the middle cerebellar peduncle. (B,C) Brain MRI (T2 excitation, fluid-attenuated inversion recovery axial scan). The lesion is located in the dorsal portion of the upper pons (B) and lower midbrain (C). Note the involvement of the upper cerebellar peduncle (arrow) and the inferior colliculus (arrowhead). (D) Axial anatomic drawing corresponding to the upper pons. The ischemic lesion (dark area) involves the right trigeminothalamic tract, the right superior cerebellar peduncle, the lateral lemniscus, and the gustatory lemniscus.

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