Statin-associated exacerbation of myasthenia gravis

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Myasthenia gravis (MG) can be exacerbated by a variety of medications, which increase weakness by interrupting neuromuscular junction transmission. Statins, which lower lipids by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, are not commonly known to worsen MG or have activity against the neuromuscular junction.1 One report suggested that statin therapy produced ocular myasthenia.2 However, based on the case description, it is not clear that this patient had MG.3 We present a patient with well-documented MG who experienced worsening of his condition after taking different statins on four separate occasions.

Case report. A 55-year-old man with hyperlipidemia and borderline hypertension was evaluated for a 1-year history of intermittent dysarthria. He first noticed dysarthria ~1 week after the initiation of atorvastatin. At that time, MRI and blood work revealed no evidence of a stroke or elevation in his creatinine kinase (CK) level. He stopped atorvastatin, and within 1 week the dysarthria resolved. During the next 5 months, he tried three other statins (lovastatin, pravastatin, and simvastatin). With each statin, the dysarthria returned in ~1 week and resolved after stopping the medication. There was no elevation in his CK after the use of any of the statins. When he sought treatment in our medical center, he had experienced several weeks of dysarthria despite avoiding statin therapy for the previous 4 months. The dysarthria was worse in the evening and after prolonged periods of talking. On examination, he was markedly dysarthric. He had normal tongue movements and was not hypophonic. No cranial nerve abnormalities or proximal muscle weakness was detected. Repetitive nerve stimulation abnormalities were consistent with MG. The facial nerve showed a 50% decrement at baseline and >50% decrement at 30, 60, 120, and 180 seconds postexercise. The ulnar nerve showed a 6 to 7% decrement, and the spinal accessory nerve showed a 10 to 12% decrement postexercise. His acetylcholine receptor antibody level was >7.5 nmol/L (normal, <0.4 nmol/L). EMG did not reveal a myopathy, and CT of the chest did not show a thymoma. He was started on pyridostigmine (60 mg TID) and experienced rapid improvement in his speech.

Discussion. To our knowledge, the only report in the literature associating statin use with worsening myasthenic symptoms involved a patient who developed ocular and systemic weakness on four separate occasions: three times with statins and once with a fibrate.2 However, it is not clear that this patient had MG because no laboratory testing verified the diagnosis.2 Our patient’s history, repetitive nerve stimulation results, acetylcholine receptor antibody levels, and response to pyridostigmine substantiate the diagnosis of MG. It appears likely that statin use exacerbated his symptoms, given that dysarthria occurred on four separate occasions after four different statins, and each time he improved after discontinuation of the medication.

Medications that exacerbate MG are thought to interrupt transmission in the neuromuscular junction. Statins, which block HMG-CoA reductase, are not known to interfere with neuromuscular junction transmission,1 but we propose three ways that statins could potentially worsen MG. First, it is now understood that statins have immunomodulatory properties, including the ability to induce production of the Th2 cytokines interleukin (IL)-4, IL-5, and IL-10.4 Animal and human studies suggest that these Th2 cytokines play a role in the development of MG;2 therefore, it is possible that by up-regulating Th2 cytokine production, statins could lead to worsening MG.

Second, statins have been postulated to cause mitochondrial dysfunction by depleting endogenous coenzyme Q10.5 The presynaptic nerve ending and the postsynaptic junction are rich in mitochondria. For this reason, statin-induced mitochondrial dysfunction could interrupt transmission in the neuromuscular junction and worsen MG.

A third theory is that a statin myopathy could exacerbate the underlying weakness of MG. Myopathy is a well-described side effect of statins, and it ranges from mild without CK elevation to overt rhabdomyolysis. It is possible that in addition to having MG, the patient described in our case also experienced a statin myopathy. This dual-hit hypothesis may explain why the association between statin use and exacerbation of MG has not been extensively documented.

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References


The fragile X premutation presenting as postprandial hypotension

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The fragile X-associated tremor/ataxia syndrome (FXTAS) is a neurodegenerative disorder consisting of progressive intention tremor and cerebellar ataxia recently described in men with the premutation (55 to 200 CGG repeats) in the promoter region of the fragile X mental retardation 1 (FMR1) gene1 and with grandchild ren with fragile X syndrome (FXS).2 We describe here a patient with postprandial hypotension and intention tremor carrying an FMR1 premutation allele and without a family history for FXS.

Case report. A 73-year-old man was referred to our clinic for episodes of blurred vision, dizziness, and weakness appearing after meals and associated with low blood pressure (BP) values.

These episodes began 1 year before our visit, but the patient also had bilateral hand tremor with onset at age 71 years, mostly pronounced with posture and action. His family history was unremarkable for peculiar neurologic disorders: he had two healthy sons aged 42 and 39 years and two healthy grandchildren. Moreover, he had only two sisters: one died at age 38 years during delivery, and the other died at age 80 years from bronchopneumonia and had healthy children and grandchildren (two males and one female). Neurologic examination revealed facial hypomimia and mild asymmetric (left greater than right) postural tremor in the distal upper extremities, which increased by action (without resting tremor). Tone, strength, sensation, deep tendon reflexes, and plantar responses were normal. There was no ataxia, and stance and gait were normal, including tandem gait. A general cognitive screen was normal (Mini-Mental State Examination score >25/30), but speller memory and problem-solving function deficits could not be excluded because a more complete neuropsychological testing was not done. EEG, EMG, and nerve conduction studies were normal, as was sympathetic skin response recorded.
from the hands after median nerve stimulation. Brain MRI revealed only moderate cortical atrophy without any signs of white matter disease. General physical examination was normal, without sexual or urinary disturbances, except for mild orthostatic hypotension with a decrease in systolic BP of 20 mm Hg when changing from a lying to a standing position. Moreover, a 24-hour BP profile (figure) showed a reversed circadian BP rhythm with higher nighttime than daytime values and after each meal a decrease of systolic BP ranging 40 to 65 mm Hg without a compensatory increase in heart rate; these changes of systolic BP were associated with dizziness and blurred vision, lasting a couple hours after meals and were interpreted as postprandial hypotension. Cardiovascular examinations, including EKG with transesophageal stimulation and study of R-R interval variability during deep breathing, echocardiography, and Doppler ultrasound studies of the carotid and verteobasilar systems, were otherwise normal. The administration of midodrine (2.5 mg TID) decreased postprandial symptoms. The molecular analysis of FMR1 gene revealed a premutation carrier status with 73 CGG repeats.

Discussion. The clinical presentation of this patient, who had severe postprandial hypotension associated with mild postural and intention tremor and who was carrying an FMR1 premutation, is atypical for FXTAS. Cases of FXTAS described thus far have consisted of intention tremor and/or ataxia, variously associated with cognitive decline, peripheral neuropathy, parkinsonism, and autonomic dysfunction; moreover, MRI showed generalized brain atrophy and/or T2 hyperintensities of the middle cerebellar peduncles, although the absence of this sign is not unusual, being present in only 59% of patients with FXTAS. Most important, all the reported cases of FXTAS were identified from families with known cases of FXS. Nevertheless in our patient, even if a family history for FXS was absent, a clinical diagnosis of "possible" FXTAS could be made because, in addition to the mandatory criterion of the FMR1 premutation status, he had intention tremor (one clinical major criterion) and moderate brain atrophy (one radiologic minor criterion). However, his main disturbances were postprandial symptoms caused by decreases in BP after meals; moreover, he had a reversed circadian BP rhythm and a mild orthostatic hypotension. This autonomic profile, although nonspecific, could identify an autonomic impairment, such as the dysfunction occurring in atypical Parkinson disease or multiple system atrophy. This autonomic dysfunction has not been previously described in patients with FXTAS, in whom dysautonomia has been mainly reported as impotence, hypertension, or bladder dysfunction.

There is growing evidence that the clinical phenotypes of FXTAS may be more heterogeneous than previously thought. FMR1 premutations have been reported in patients with essential tremor and/or in cases of sporadic ataxia without a family history for FXS. Our report adds further evidence to the clinical spectrum of FXTAS and suggests that DNA testing for the FMR1 premutation may reveal additional carriers among patients with BP dysautonomia. Nevertheless, further studies on more FMR1 premutation carriers are needed to confirm whether BP dysautonomia is a clinical feature of these subjects.

Heterozygous Niemann-Pick disease type C presenting with tremor

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Tremor is defined as rhythmic oscillation of a body part. The differential diagnosis of tremor is extensive; however, when there is a family history of tremor, the diagnosis most likely will be essential tremor. We describe a woman who sought treatment for tremor, had a family history of tremor, and was found to have a unique diagnosis.

Case report. A 75-year-old woman was referred to the neurology department with a 10-year history of tremor, initially a side-to-side head tremor. Five years after onset, her tremor had progressed, involving her right hand and 1 year later, the left. The tremor in her upper extremities predominantly occurred at rest; however, she also stated that occasionally she would experience a tremor in her hands while holding a cup of coffee or a deck of cards. She carried a diagnosis of Parkinson disease, but her tremor did not improve with 1,000 mg of l-dopa/carbidopa therapy, which she took for 3 months. Her family history was interesting because three brothers all developed tremor and an incurable neurologic disease. Her neurologic inventory was otherwise negative.

On examination, she was jocular. On the Short Test of Mental Status, she received a score of 31 of 38. Her cranial nerve examination was normal. She had a continuous “no-no” head tremor and a mild overactive tongue. With her arms in a position of partial repose (e.g., with her left elbow on the armchair and her hand on her lap), she developed a severe tremor. Her gait was unremarkable, except for a moderate overactive gait of both upper extremities. Her medical examination, including abdominal examination, was unremarkable. A complete

Figure. A 24-hour noninvasive ambulatory recording of blood pressure and heart rate. Systolic blood pressure values are on the top (continuous line); diastolic blood pressure values are in the middle (dashed line); and heart rate values are on the bottom (dotted line).
blood count was normal, except for the platelet count, which was 93 × 10^9/L (normal, 150 to 450 × 10^9/L). Peripheral blood smear revealed normal platelet morphology but clumping. Her thyroid and liver function studies, serum ceruloplasmin, and 24-hour urine copper collection were normal. A lactic acid level was elevated at 2.0 mmol/L (normal, 0.93 to 1.65 mmol/L). An abdominal ultrasound revealed diffuse fatty infiltrate of the liver and normal spleen size. MRI head scan revealed patchy increased T2 signal changes in the white matter of both cerebral hemispheres consistent with chronic small vessel ischemic changes.

A multichannel EMG recording initially revealed no resting tremor and an occasional postural 5-Hz tremor in the left arm. With mental activation, however, she developed a high amplitude synchronous 4- to 5-Hz tremor in both hands that disappeared immediately after the alerting procedure was discontinued. The findings were consistent with a parkinsonian tremor.

Spinoocerebellar ataxia panel, cholesterol esterification, filipin staining, and sphingomyelinase were normal. We reviewed the original article on the patient’s brothers. Three brothers had a childhood-onset disorder characterized by tremors, dysarthria, gait ataxia, dementia, spasticity, and vertical supranuclear gaze palsy (VSGP). The tremors occurred only under stressful situations and were not found on examination. Since publication of that article, a bone marrow aspirate completed in 1981 on the youngest brother (III-28) showed cells suggestive of sea-blue histiocyties. Therefore, we proceeded to genetic testing for Niemann–Pick disease type C (NPC). Our patient was found to be a carrier for one mutation within the NPC1 gene. In exon 20, there was a 2974G→C mutation changing glycine→arginine at position 992 (GGG→CGG), indicating that our patient is a carrier for NPC and supporting the clinical suspicion of NPC in her brothers.

Discussion. NPC is an autosomal recessive disease characterized by dementia, ataxia, VSGP, and splenomegaly. Adults may have psychosis, but adult onset is rare. Our patient is a carrier of one mutation of the NPC gene. Heterozygous carriers of NPC have not been reported to have neurologic symptoms. However, the finding of this known mutation is suggestive of the cause of our patient’s neurologic disease. The absence of dementia, VSGP, and spasticity at age 73 years is most likely because she only carries one mutation.

In a recent review of 16 patients with adult-onset NPC, tremor was not found, making this patient and her family unique in terms of presenting and progressive signs. The characteristic of the upper extremity tremor noted in our patient is in keeping with a parkinsonian tremor. This was the clinical suspicion that was corroborated by multichannel EMG recording.

Heterozygous NPC may have neurologic disease and should be considered in the differential diagnosis of patients with a parkinsonian tremor.

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References

Radicular myoclonus induced by repetitive neck movements in a patient with cervical spondylosis

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Myoclonus results from abnormal activity in many different parts of the CNS. Only a few cases of peripheral nervous system-generated myoclonus have been reported in patients with spinal root lesion. We report a patient who developed a cervical segmental myoclonus immediately after prolonged repetitive flexion-extension neck movements.

Case report. A 67-year-old man developed neck pain and tension. In an attempt to reduce neck tension, he started to perform repetitive flexion-extension neck movements for 10 minutes every morning. After a few days, he developed involuntary jerking of the right shoulder immediately after repetitive flexion-extension neck movements. The general practitioner, who thought that this was a simple partial seizure, injected the patient with 2 mg diazepam ~30 minutes after the onset of symptoms and again 2 hours later, but the treatment was ineffective.

The patient arrived at our emergency department 6 hours later. On examination, he had rhythmic, involuntary jerks of the right shoulder on the horizontal plane and a slight lateral flexion of the head on the right side. Neurologic examination was otherwise normal. The involuntary activity was not affected by neck movements or by distraction or mental concentration. Blood count and chemistries (glucose, liver and renal function tests, electrolytes, and B12 level), rheumatologic screen (erythrocyte sedimentation rate, antinuclear antibody, anti-DNA, rheumatoid factor, complement factors C3 and C4, and anticardiolipin antibody), copper and ceruloplasmin concentration, and thyroid function were normal. The EEG was normal. However, during activation with hyperventilation, the ongoing involuntary activity increased in frequency and amplitude in the absence of EEG modification.

EMG recording revealed cocontraction of several muscles with synchronous repetitive discharges of motor units occurring in trains lasting several minutes in right pectoralis major (clavicular head), teres major, pronator teres, and intermittently in biceps and brachioradialis muscles (all supplied by the C6 root). The involuntary activity in the neck muscles originated from a deep muscle and was not documented with EMG, but it is conceivable that it originated from the longus colli muscle that produces lateral flexion of the head and is supplied mainly by the C6 root. The duration of bursts of activity ranged from 350 to 410 ms. Subsequent recordings showed two different rates of involuntary movements, either 0.5 or 1.7 Hz. Hyperventilation either precipitated the involuntary activity or increased the amplitude of ongoing involuntary movements. When the frequency of involuntary movement was 0.5 Hz, it changed to 1.7 Hz after hyperventilation. No signs of denervation were found. The blink reflex and its recovery cycle were normal. Motor evoked potentials and somatosensory evoked potentials (SEPs) after stimulation of radial, median, and ulnar nerve were normal. The recovery cycle of the spinal SEPs evoked by pairs of stimuli to the radial nerve, which distributes to the C6 and C7 dermatomes, was normal. This test may reveal excitability changes within the dorsal horn in segmental myoclonus of spinal origin. Cervical cord MRI revealed that the right C6 neural foramen was narrowed because of degenerative spondyloitic changes, the spinal cord being normal.

The patient stopped the morning stretching activity of neck muscles. The movements resolved in the next 3 days. The patient did not have sensory symptoms. The cerebrospinal fluid involving C6 myotome, the MR evidence of narrowing of the right C6 neural foramen, together with the absence of any excitability change in cerebral cortex, brainstem, or spinal cord suggest that the jerks...
The rarity of radical myoclonus contrasts with the high incidence of radiculopathies, and it is possible that a genetic or other factor may contribute to its development.

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References


Primary respiratory failure in inclusion body myositis

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The idiopathic inflammatory myopathies are a group of disorders characterized by acquired muscle weakness and presence of inflammatory infiltrates in skeletal muscle.1 2 The three most common diseases within this group are dermatomyositis (DM), polymyositis (PM), and inclusion body myositis (IBM). Respiratory muscle weakness with respiratory failure is a well-recognized complication in PM and DM but has only rarely been reported in IBM.3 4 Symptomatic respiratory failure in IBM is considered to be secondary to coincidental pulmonary disease.5 We report a patient with IBM who developed subacute respiratory failure caused by primary respiratory muscle weakness.

Case report. A 58-year-old woman sought treatment for slowly progressive muscle weakness, dysphagia, and weight loss. Her medical history was unremarkable, and she did not use any myotoxic drugs. Physical examination revealed normal speech, mild facial weakness, dysphagia without aspiration, and generalized muscle weakness (Medical Research Council [MRC] score, 4) with asymmetric weakness of the forearm muscles (right, MRC 4; left, MRC 3). Muscle atrophy was most pronounced in the peroneal muscles where the circumference was mildly increased (285 U/L; normal, <180 U/L). Nerve conduction studies were normal. EMG demonstrated spontaneous activity and a mixed pattern of short-duration low-amplitude and long-duration high-amplitude motor unit potentials at submaximal voluntary contractions. By EMG, forearms flexor muscles were more involved than forearm extensor muscles. Muscle biopsy from the anterior tibial muscle revealed a small number of muscle fibers surrounded by collagen, fat cells, and inflammatory infiltrates. IBM was diagnosed according to established criteria,6 and the patient was referred to a rehabilitation clinic.

Eight months after initial presentation, she gradually developed shortness of breath on exertion. She subsequently experienced fatigue, decreased daytime, sleepiness, and confusion. One day she was found unconscious as a result of severe hypoxemia and required intubation and mechanical ventilation. Arterial blood gas analysis after intubation showed elevated PCO2 (7.9 kPa = 806 mm H2O) and bicarbonate (33.7 mmol/L), reflecting chronic hyperventilation. Ancillary investigations showed no signs of cardiac disease or respiratory infection. Initially, nighttime apneas occurred lasting up to 45 seconds with hypercapnia (PCO2 8.2 kPa = 836 mm H2O) and elevated bicarbonate (34.8 mmol/L), after which mechanical ventilation was adjusted. Apparently, the respiratory drive in our patient was depressed during sleep. This probably resulted from bicarbonate retention and sleep deprivation caused by frequent arousals during REM sleep because of hypercapnia.7 Her general condition improved, and the need for daytime ventilatory support decreased. She underwent tracheotomy and thereafter required volume-regulated ventilation for 2 hours in the afternoon and at night. Two months after admission, she was discharged home on continued mechanical ventilation.

The presence of severe respiratory failure made us reconsider her diagnosis. Empirical treatment with prednisone (50 mg daily for 4 weeks) resulted in minimal increase in muscle strength. Nerve conduction studies of the phrenic nerve demonstrated low amplitudes of the compound motor action potential of the diaphragm bilaterally. EMG revealed poor recruitment without spontaneous activity of the diaphragm and intercostal muscles. Muscle biopsy from the tibialis anterior showed myopathic changes with invasion of non-necrotic muscle fibers by mononuclear cellular infiltrates, basophilic rimmed vacuoles, and sarcocellular HLA- Class II positivity of all muscle fibers, consistent with the diagnosis of IBM8 (figure). Pulmonary function testing revealed mildly impaired vital capacity (1.87 L; normal, 2.60 L) and decreased mouth pressures (maximal expiratory pressure, 3.01 kPa = 307 mm H2O; normal, 8.90 kPa; maximal inspiratory pressure, 1.90 kPa = 193 mm H2O; normal, 6.90 kPa), reflecting an extraparenychymal restrictive pattern. It was concluded that the patient had IBM9 with primary respiratory muscle weakness, which had resulted in primary respiratory failure.

Discussion. Respiratory failure in patients with IBM is generally believed to occur only secondary to aspiration pneumonia or coincidental pulmonary or cardiac disease.5 Primary respiratory failure has, to the best of our knowledge, been reported only twice in literature.10 One of these reported patients had a concomitant activated human T-cell lymphotropic virus type 1 infection.4 In our patient, respiratory failure resulted from hyperventilation caused by weakness of the diaphragm and intercostal muscles. Our limited awareness of this manifestation of IBM delayed its recognition.
and resulted in life-threatening respiratory failure. Only then the ventilatory support was started, and the vicious circle of respiratory muscle weakness, hypoventilation, hypercapnia, sleeping problems, deterioration of the general condition, weight loss, and severe respiratory failure was broken. Moreover, we started high-dose corticosteroid treatment, which involves a risk of serious adverse effects. In conclusion, primary respiratory failure can occur in patients with IBM, and awareness of this potentially life-threatening complication is warranted, especially for patients with signs and symptoms suggestive of hypoventilation.

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References

Alopecia and cutaneous atrophy after greater occipital nerve infiltration with corticosteroid

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Greater occipital nerve (GON) infiltration is used as a treatment for patients with primary and secondary headache disorders, including migraine and cluster headache. This procedure has several advantages, including ease of performance and a relative lack of complications. As the physiology of the trigeminocervical neurons is better understood and possible brain modulatory roles of greater occipital nerve stimulation are explored, the procedure may gain increased usage. In our experience, GON infiltration is highly efficacious for certain patients, particularly those with tenderness over the nerve, and it remains a valuable intervention for the management of headache disorders. It is generally without side effects. Here we report two cases in which the procedure has been complicated by a previously unreported side effect of alopecia and cutaneous atrophy. These patients represent 2 of the last 100 patients we have injected for various headache indications.

Case reports. Case 1. A 27-year-old man sought treatment for a history of headaches from childhood consistent with a diagnosis of migraine with aura. He now had chronic daily headache, assuming compound analgesic preparations daily. On examination, he had tenderness in the region of the right GON. A nerve block was performed with 80 mg methylprednisolone acetate in 2 mL and 3 mL of 2% lidocaine, resulting in anesthesia.
of the right posterior aspect of the head. He subsequently enjoyed a headache-free period lasting 3 months. The only side effect reported was hair loss at the site of the injection. Three small, but conspicuous, round patches of alopecia were noted. Each was ~1 cm in diameter and was associated with marked cutaneous atrophy. These patches are still present 11 months later.

Case 2. A 55-year-old woman sought treatment for a 2.5-year history of left occipital headache that was diagnosed as migraine without aura. A left GON infiltration was performed using the same technique and compounds as in Case 1, which resulted in a complete resolution of her symptoms for 4 days. No side effects were reported. The procedure was repeated 6 months later because it had been the only intervention to afford any symptomatic relief. Unfortunately, the benefit on the second occasion was less conspicuous, round patches of alopecia were noted. Each was ~1 cm in diameter and was associated with marked cutaneous atrophy. These patches are still present 11 months later.

Discussion. We describe alopecia with underlying fat atrophy after GON infiltration with lidocaine and depo-corticosteroids for the management of primary headache. This is a commonly used procedure in headache clinics, and patients and clinicians need to be aware of this possible complication. Although corticosteroids are not universally used during GON blockade, relief of headache may be prolonged after their use.1 This issue now needs to be revisited and defined for each headache type treated so the real risk-benefit assessment can be made.

A variety of corticosteroid preparations and doses have been used,1,2,3 but this side effect was not reported. The estimated occurrence of cutaneous atrophy after corticosteroid injection ranges from 1 to 14%,6 although there may be under-reporting. It appears to be more common in premenopausal women.7 Mixing corticosteroids with other solutions, such as saline or local anesthetic, should only be done if the solutions are miscible—if solubility is altered, it may result in a subcutaneous depot injection. Resolution of cutaneous atrophy is reported to occur after 6 to 7 months, although it may persist up to 24 months.2 GON infiltration is undoubtedly an effective and useful treatment for certain patients. At times, it may be the only intervention to offer a patient symptomatic relief. There are currently no firm guidelines concerning patient selection or clinical features predictive of a successful outcome. There is no clear consensus on the efficacy of the procedure itself. However, given the lack of severe side effects associated with GON infiltration, it should still be considered as a useful therapy for the management of headache pain. We have described two examples of this novel complication, alopecia with fat atrophy, in a relatively small series of patients. In light of this, we would suggest that all patients, especially women, should be advised of this cosmetic side effect when consenting to the procedure. Moreover, it seems inadvisable in general to inject the supraorbital nerve unless there is a specific indication to do so.

Figure. An example of alopecia with fat atrophy after local injection of the area of the greater occipital nerve with 2% lidocaine and 160 mg methylprednisolone for headache.

Middle interhemispheric variant of holoprosencephaly: A very mild clinical case

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Middle interhemispheric variant (MIH) of holoprosencephaly or syntelencephaly was described in 19931 as a fourth subtype of holoprosencephaly (HPE), in addition to the three classic types of alobar, semilobar, and lobar HPE.2 MIH consists of an abnormal midline continuity of the posterior frontal and parietal regions of the cerebral hemispheres, with separation of the basal forebrain, anterior frontal lobes, and occipital regions. Although MIH and classic HPE share a number of similarities, they are related to different embryologic mechanisms. Classic HPE is caused by a defect in the formation of the embryonic floor plate, whereas MIH is secondary to a disturbance of formation of the roof plate.2 The ZIC2 gene plays a critical role in differentiation of the roof plate of the developing embryo in the dorsal midline of the neural tube.3 In mice, decreased levels of ZIC2 result in the failure to form midline CNS structures. In humans, mutations in the ZIC2 gene have been found in ~3 to 4% of HPE cases, including individuals with MIH, confirming that MIH is a variant of HPE.4 The clinical manifestations of MIH patients have been recently reported in detail and compared with classic HPE.5 Neurologic developmental functions were similar to the lobar subtype of HPE.

References

Revised scale was normal (total IQ, 103; performance IQ, 101; verbal IQ, 106).

In particular, speech and oromotor development were delayed in all MIH cases; mild to moderate spasticity, hypotonia, and dystonia occurred in a high percentage of cases, as did seizures. Facial dysmorphisms were moderate or even mild. Severe midline craniofacial anomalies, choreoathetosis, and endocrine dysfunction were absent in MIH cases.

Case report. A 14-year-old boy was referred to us because of muscular hypotonia and weakness. He is the first child of healthy, nonconsanguineous parents. He was born at term after an uneventful pregnancy with normal delivery. Birth weight was 2,800 g. Motor development was slightly delayed (unsupported walking acquired at age 18 months). He never had seizures. Despite the presence of a mild reading disorder, his academic skills were within the normal range.

Neurologic examination showed no facial dysmorphism (namely, no hypotelorism or hypertelorism or single central maxillary incisor), normal head circumference, mild weakness of eye closure, a slightly reduced muscular tone and trophism, rigid spine, proximal limb weakness mainly of the shoulders, and normal osteotendinous reflexes. He was able to walk independently with lordosis. Cardiac and respiratory functions were apparently normal. Endocrine functions and temperature regulation were normal.

Laboratory investigations, including creatine kinase, transaminases, and karyotype, were normal. EKG was normal. EMG (deltoid muscle) showed myogenic signs. Nerve conduction velocity was normal. Muscle biopsy of quadriceps revealed only mild myopathic changes, as increasing of the percentage of central nuclei and type I fiber predominance, without specific degenerative or inflammatory features.

IQ assessed with the Wechsler Intelligence Scale for Children—Revised scale was normal (total IQ, 103; performance IQ, 101; verbal IQ, 106).

In conclusion, this case contributes to the further definition of the phenotype of MIH, indicating that the clinical variability of this disorder is wider than expected, also including a very mild clinical phenotype.

Brain MRI revealed a middle interhemispheric variant of holoprosencephaly (figure).

Genetic analysis for sonic hedgehog was not performed. Results of mutational analysis for ZIC2 gene are not yet available.

Discussion. The severity of HPE correlates with the degree of neurologic impairment and developmental delay. In the most severe type (lobar), there is only a minimal developmental progress, whereas the developmental outcome is more favorable in milder forms of HPE (semilobar and lobar). Despite similarities with lobar HPE, MIH represents a distinct cliniconeuroradiologic subtype of HPE. The frequency of seizures, hypotonia, and dystonia was comparable, whereas spasticity occurred more frequently in MIH than in lobar HPE. Developmental neurologic abnormalities, including mobility, upper extremity function, and expressive language, were similar to those of lobar HPE. The degree of dysfunction of these variables has been correlated with the nonseparation of deep gray nuclei (caudate, lentiform nuclei, and thalamus). Language development is poor in lobar HPE and MIH, and patients are usually able to pronounce only single words or short sentences.

However, expressive language and intelligence of our case are completely normal, and his academic skills are in the normal range, except for a mild reading disability.

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References


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