Gold myokymia syndrome

A rare toxic manifestation of chrysotherapy[1]

Paul H. Caldron, D.O.[2]
Asa J. Wilbourn, M.D.
Emmanuel E. Bravo, M.D.
Hiroshi Mitsumoto, M.D.

Neurological complications of gold therapy appear to be uncommon. The authors report the second of two patients with rheumatoid arthritis seen at the Cleveland Clinic who experienced a particularly rare and largely unknown reaction to gold consisting of myokymia and dysautonomic symptoms (gold myokymia syndrome). Myokymia is a peculiar rhythmic rippling of muscles that must be distinguished from other forms of spontaneous muscle activity. The clinical and electrophysiologic characteristics of this problem, which consistently resolves with cessation of gold administration, are discussed. Because gold therapy remains a prominent modality in the management of rheumatoid arthritis, increased awareness of this adverse reaction is necessary.

Index terms: Gold • Neurologic manifestations

Cleve Clin J Med 54:225–228, May/June 1987

Neurological complications of intramuscular gold therapy for rheumatoid arthritis (RA) are not frequently recognized among the variety of potential adverse reactions.[1] Two patients with RA, one previously reported[2] and the other the subject of the following case report, experienced a rare but well-documented adverse reaction to chrysotherapy that we call gold myokymia syndrome (GMS).[3–6] The features of GMS typically include myokymia, various dysautonomic symptoms such as sweating, hypertension with positional changes, and tachycardia, plus affective symptoms such as insomnia, emotional lability, depression, and even psychosis. Fatigue and weight loss are frequent accompanying constitutional symptoms.[3,4] Myokymia, which appears as a continuous, undulating, wormlike rippling of muscle, has a characteristic appearance on electromyography; the myokymic discharges seen with GMS are grouped action potentials, which fire spontaneously and repetitively, in a regular fashion. They are readily differentiated from the sporadically firing spontaneous discharges called fasciculation potentials, which occur with other neurologic disorders such as amyotrophic lateral sclerosis (ALS).

We believe this form of toxicity should be recognized by clinicians employing chrysotherapy, as well as neurologists and psychiatrists, because of its attendant morbidity and its resolution with cessation of therapy. In addition, since the presentation of GMS may suggest other disorders such as ALS, pheochromocytoma, or severe

[1] Departments of Rheumatic and Immunologic Disease (P.H.C.), Neurology, (A.J.W., H.M.), and Research (E.L.B.), The Cleveland Clinic Foundation. Submitted for publication Sep 1986; accepted Nov 1986.

[2] Present address: Department of Medicine, Evanston Hospital, Northwestern University, McGaw Medical Center, Evanston, IL.

0891-1150/87/03/0225/04/$2.00/0

depression, as illustrated by these cases, prompt recognition of the syndrome may help to avoid misdiagnosis and unwarranted investigations and treatments.

Case report

This 65-year-old Caucasian male was in good health until September 1982 when he began to experience mild symmetric, diffuse joint aches. Initial treatment included various analgesic antiinflammatory drugs. In early December 1982, over a period of approximately one week, symmetric polyarticular synovitis developed, with two hours of morning joint stiffness in a typical rheumatoid distribution. There were no other systemic rheumatic symptoms. The RA latex fixation test initially measured 1:10,000. He was hospitalized at that time for bed rest and physical therapy, and treatment was begun with enteric coated aspirin 4.8 g daily and myochrisine 50 mg weekly intramuscularly after incremental test doses.

By March 1983, following an approximate total myochrysine dose of 500 mg, his joint symptoms and morning stiffness had markedly improved. However, he began to develop increasing fatigue, night sweats, disturbed sleep pattern, mild hypertension with orthostatic drop, depression, generalized fine involuntary muscle rippling, and a nonpruritic erythematous rash. A skin biopsy showed nonspecific inflammation in the dermis. The rash resolved over a period of ten days, and myochrysine was continued. In April 1983, the patient was seen by a psychiatrist for depression; electroconvulsive therapy was recommended, but refused. In May 1983, because of onset of hypertension and the above associated symptoms, he was referred to the Cleveland Clinic for evaluation of suspected pheochromocytoma.

Physical examination revealed mild resting tachycardia and tachypnea. Blood pressure was 168/82 mmHg supine and 130/98 mmHg standing. The skin was cool and diaphoretic without rash. No active synovitis, joint deformity, or joint restriction were present. Continuous vermiform muscle twitching in all extremities and tongue were visible and mild generalized weakness was noted. Sensation and reflexes were normal. His affect was depressed and he conveyed feelings of hopelessness.

Liver and renal functions, CPK, complete blood count, chest radiography, and electrocardiography were unrevealing. Serum catecholamines, clonidine suppression test, abdominal computed tomography, and arteriography showed no evidence of pheochromocytoma, and magnetic resonance imaging demonstrated normal cranial and foramen magnum structures. Routine cerebrospinal fluid values were normal; gold concentration was 0.7 μg/dL. ALS was initially suspected because of the continuous fine involuntary muscle movement. However, an extensive electromyographic examination showed normal routine nerve conduction studies, widespread myokymic discharges on needle electrode examination, and absent H-reflexes. Fasciculation potentials were not seen. Because of experience with the previously reported case,[2] the correlation of this myokymia with the use of gold was recognized by the electromyographer.

Right vastus lateralis muscle biopsy findings revealed small angular fibers with some degeneration, increased acetylcholine esterase content and glycogen stores, and no inflammation, consistent with neurogenic atrophy.

Although cold pressor and hyperventilation responses were normal, autonomic insufficiency was confirmed by a blocked Valsalva response, as well as an abnormal tilt test and amylnitrite and phenylephrine response slopes. Myochrysine therapy, which had reached a cumulative dosage of approximately 700 mg, was discontinued. Carbamazepine 200 mg tid administered orally markedly reduced the myokymia and diaphoresis, but was electively discontinued after two weeks. Over the next four months, all autonomic and affective symptoms as well as myokymia resolved. Tilt test response returned to normal. His arthritis remained dormant during this period with no medication.

Discussion

The clinical features observed in this patient closely parallel those of our first patient, a 30-year-old man who after having received 1200 mg of gold sodium thiomalate for the treatment of RA also experienced myokymia and dysautonomic symptoms. His myokymia disappeared during a three-week course of carbamazepine, returned when that medication was discontinued, and subsequently the myokymia and dysautonomic symptoms resolved within two months of cessation of gold therapy.[2] Indeed, before electromyographic examination, that patient's neurologist also had suspected ALS.

In 1934, Chavany and Chaignot[3] first reported the occurrence of a symptom complex of myokymia, sweating, and mental symptoms in association with gold therapy, in an era when this metal was used as an antimicrobial agent. The French literature (almost exclusively) contains many early reports of gold-related myokymia, as well as motor-sensory neuropathies, mental status changes, and seizures.[4] In 1958, Endtz[7] reviewed 72 cases of neurotoxicity related to the use of gold and categorized them into four groups: a Guillain-Barré-like syndrome of peripheral (predominantly motor) neuropathy; a severe burning neuropathy associated with anxiety and insomnia; an encephalopathy with various mental changes and organic psychoses; sporadic symptoms, radicular involvement, and tics. Generalized myokymia may occur as an additional feature in at least the first three of these categories, and, as in our experience, in concert with several dysautonomic symptoms, generalized weakness, and organic depression.[5,6] Such reports are virtually confined to the neurological literature. Rheumatic disease texts bear little mention of neurotoxicity from the use of gold, and prominent psychiatric texts do not list gold among metals associated with depression or psychoses.[1,8]

These two cases of GMS may represent the first two reported from the United States, although in 1977, Furst et al[9] reported a patient who had received high-dose gold therapy and experienced a "previously unreported" complication of an ALS-like syndrome, which we suspect may have been GMS. Schlumpf et al[10] recently reported a patient with Guillain-Barré-like weakness and fasciculations who was HLA-DR3 positive, an antigen that may be associated with susceptibility to other forms of gold toxicity.[11]

The incidence of gold neurotoxicity quoted at 0.5% to 15% during the 1930s and 1940s seems unrealistically high for current chrysotherapy practices, though later figures have not been established.[12,13] GMS appears to be distinctly rare. No relationship of GMS with demographic parameters or disease duration has been identified. Myokymia has been reported with as little as 400 mg total dosage, but generally develops when the cumulative dose is 1 to 2 g. A variety of intramuscular preparations have been implicated; no cases of GMS have been reported with newer oral preparations.[10,14,15] Most reports have described patients with mild to moderate rheumatoid disease uncomplicated by vasculitis or Felty's syndrome. Cutaneous and hematologic reactions may herald the onset of GMS.[10]

In the earlier case reported, random serum gold levels ranged from 25 to 36 μg/dL; in the case presented herein, serum levels were not obtained, but a cerebrospinal fluid level of 0.7 μg/dL was determined. A usual therapeutic range of serum gold has been suggested (38 to 500 μg/dL), but no such range for central nervous system gold has been established. It should be noted, however, that several studies have failed to demonstrate a correlation of blood level of gold either with clinical response or with any form of toxicity.[11,16,17] Gottlieb et al[18,19] have shown that muscle is one of the tissues that has a relatively low gold concentration during therapy, and that in other tissues such as skin, hair, and nails, gold contents were no different in those without toxicity from those with toxicity, such as gold dermatitis.

Motor and sensory nerve conduction studies may be normal, as in our cases and in isolated myokymia, or may be abnormal in the presence of other neuropathologic features.[5,6,10,20] H-reflexes may be absent. Needle electrode examinations typically reveal continual volleys of doublets, triplets, and multiplets in many muscles, particularly in the lower extremities. These are sometimes accompanied by fasciculation potentials, but not fibrillation potentials. Myokymic discharges are a type of spontaneous activity seldom seen in the EMG laboratory. They occur focally with radiation-induced plexopathies, and in a more generalized distribution as one component of Isaac's syndrome.[20,21] Myokymia has also been reported in association with mercury intoxication.[22]

Although there is no pathognomonic lesion, sural nerve biopsies have demonstrated a pattern of demyelination, remyelination, regression of axons, and reduction in large myelinated fiber numbers.[6] Muscle biopsy specimens in myokymia have been characterized by angular fibers of types I and II, and stained darkly for NADH tetrazoleum reductase, suggesting denervation atrophy. Glycogen depletion may be evident in scattered fibers. Electron microscopy of a gastrocnemius specimen from our earlier patient revealed no abnormality. Neither muscle nor nerve biopsy findings have demonstrated vasculitis.[2]

Physiologic and pharmacologic studies by Meyer et al[5] in patients with GMS point to a disturbance in the peripheral effector-receptor interaction of the sympathetic and motor nervous systems. Proximal nerve blockade causes loss of reflexes, voluntary movement, and sensation, but does not ablate myokymia, while neuromuscular blocking agents do, suggesting the abnormal generators lie along the mid and/or distal portions of the peripheral nerve fibers.[2,5,23] Norepinephrine levels may rise discordantly with a postural drop in blood pressure, and the bradycardic-hypotensive response to Valsalva maneuver may be blocked, indicating loss of integrity of the baroreceptor reflex arc.[5]

The basis of therapy of GMS is cessation of gold administration. The prognosis for resolution of all gold-associated neurologic and psychiatric symptoms is good, generally within two weeks to several months.[2,4] Unlike gold-induced peripheral polyneuropathy, which, if severe, may result in permanent residua (e.g. foot drop), GMS usually clears completely once gold treatment is discontinued.[21] Carbamazapine may dramatically reduce the myokymia and some autonomic symptoms.

Awareness of this form of gold toxicity is the key to early diagnosis and avoidance of unnecessary tests and misdiagnosis.

References

1. Zvaifler N. Gold and antimalarial therapy. [In] McCarty DJ, ed. Arthritis and Allied Conditions. 9th ed. Philadelphia, Lea and Febiger, 1979, pp 355–363.
2. Mitsumoto H, Wilbourn AJ, Subramony SH. Generalized myokymia and gold therapy. Arch Neurol 1982; **39:**449–450.
3. Chavany JA, Chaignot A. Contribution à l'étude des accidents nerveux de la chrysothérapie. Presse Méd 1934; **42:**478–480.
4. Lescher FG. Nervous complications following treatment by gold salts. Br Med J 1936; **2:**1303–1305.
5. Meyer M, Haecki M, Ziegler W, Forster W, Schiller HH. Autonomic dysfunction and myokymia in gold neuropathy. [In] Canal N, Ozza G, eds. Peripheral Neuropathies. Amsterdam, Elsevier/N Holland Biomedical Press, 1978, pp 475–480.
6. Katrak SM, Pollock M, O'Brien CP, et al. Clinical and morphological features of gold neuropathy. Brain 1980; **103:**671–693.
7. Endtz LJ. Complications nerveuses du traitment aurique. Rev Neurol 1958; **99:**395–410.
8. Peterson GC. Organic mental disorders induced by drugs or poisons. [In] Kaplan HI, Freedman AM, Sadock BJ, eds. Comprehensive Textbook of Psychiatry III. Baltimore, Williams and Wilkins, 1980, pp 1437–1451.
9. Furst DE, Levine S, Srinivasan R, Metzger AL, Bangert R, Paulus HE. A double-blind trial of high versus conventional dosages of gold salts for rheumatoid arthritis. Arthritis Rheum 1977; **20:**1473–1480.
10. Schlumpf U, Meyer M, Ulrich J, Friede RL. Neurologic complications induced by gold treatment. Arthritis Rheum 1983; **26:**825–831.
11. Panayi GS, Wooley P, Batchelor JR. Genetic basis of rheumatoid disease: HLA antigens, disease manifestations, and toxic reactions to drugs. Br Med J 1978; **2:**1326–1328.
12. Hartfall SJ, Garland HG, Goldie W. Gold treatment of arthritis. Lancet 1937; **2:**838–842.
13. Sundelin F. Die gold Behandlung der chronischen Arthritis unter besonderer Berücksichtigung der Komplikationen. Acta Medica Scandinavica 1941; **67:**1–291.
14. Blodgett RC Jr. Auranofin: Experience to date. Am J Med 1983; **75:**86–89.
15. Gambari P, Ostuni P, Lazzarin P, Tavolato B, Todesco S. Neurotoxicity following a very high dose of oral gold (auranofin). Arthritis Rheum 1984; **27:**1316–1317.
16. Gottlieb NL, Smith PM, Smith EM. Pharmacodynamics of ^{197}Au and ^{195}Au labeled aurothiomalate in blood. Correlation with course of rheumatoid arthritis, gold toxicity, and gold excretion. Arthritis Rheum 1974; **17:**171–183.
17. Gottlieb NL, Smith PM, Smith EM. Gold excretion correlated with clinical course during chrysotherapy in rheumatoid arthritis. Arthritis Rheum 1972; **15:**582–592.
18. Gottlieb NL, Smith PM, Smith EM. Tissue gold concentration in a rheumatoid arthritic receiving chrysotherapy. Arthritis Rheum 1972; **15:**16–22.
19. Gottlieb NL, Smith PM, Penneys NS, Smith EM. Gold concentrations in hair, nail, and skin during chrysotherapy. Arthritis Rheum 1974; **17:**56–62.
20. Lederman RJ, Wilbourn AJ. Brachial plexopathy: recurrent cancer or radiation? Neurology 1984; **34:**1331–1335.
21. Isaacs H. A syndrome of continuous muscle-fibre activity. J Neurol Neurosurg Psychiat 1961; **24:**319–325.
22. Garcin R, Boudène C, Ginsbourg M. Chorée fibrillaire de Morvan et polyradiculonévrite d'étiologie mercurielle probable. Rev Neurol 1971; **125:**322–326.
23. Isaacs H. Continuous muscle fibre activity in an Indian male with additional evidence of terminal motor fibre abnormality. J Neurol Neurosurg Psychiat 1967; **30:**126–133.

Paul H. Caldron, D.O.
2700 Bryant Avenue
Evanston, IL 60201