Argyria: Report of a case associated with abnormal electroencephalographic and brain scan findings

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The argyria in the 83-year-old patient in this case had developed 40 years earlier secondary to the use of Argyrol brand nasal packings, which had been used for the treatment of sinusitis over a 2-year period. Discolorations of the patient's skin varied from slightly silver hues to highly pronounced silver-blue pigmentations. Computed tomographic scans revealed that the patient had ill-defined lucencies in the parietal areas of the brain bilaterally. Seizure activity of the grand mal type also was exhibited by the patient. The findings from this case are examined in light of the current literature regarding argyria. The benign nature of argyria is questioned. Causes of argyria, complications, the course of the disorder, and the efficacy of various treatments are reviewed.

Argyria results from excessive exposure to silver salts or silver protein colloids. Current thought holds that silver has very low systemic toxicity. However, because of insufficient data regarding the effects of exposure to relatively larger amounts or continued exposure to even small amounts, silver salts have been given a toxicity rating of 4. Therefore, physicians should be cautious in their use of compounds containing silver salts. Doses of 50-500 mg./kg. are lethal.¹

When silver salts are applied over the skin, localized argyria results. These same compounds, when applied to mucosal surfaces, inhaled, or injected into the body, will cause generalized argyria. In localized argyria, silver will enter the body through exocrine sweat glands and remain in the skin.^{2,3} In generalized argyria, silver is deposited first in the connective tissues of the kidney, liver, and spleen⁴ and in the eye;⁵ it also can be detected in the blood.⁶ The skin is the last organ to be af-

ected in generalized argyria.⁷

The causes of argyria are known, and the disorder is completely preventable, but argyria is still seen periodically. The use of folk remedies, overprescription of drugs containing silver, and occupational exposure to silver compounds^{5,8} (Table 1) are three important causes. Current silver-containing medications (Table 2) include silver nitrate pills for gastrointestinal ailments,⁹ nosedrops for sinusitis,¹⁰ antismoking lozenges,^{11,12} and sulfadiazine, mafenide, and sulfasalazine which are used to limit infection.^{2,13} Bladder irrigations and abdominal surgery also have been implicated in argyria. The "amalgam tatoo," permanent silver coloring on the gums around an area of a filled tooth, occurs frequently.¹⁴ It is not clear whether this phenomenon represents localized or generalized argyria.

Generalized argyria is very difficult to detect in its initial stages; it usually is not recognized until the skin starts to take on the silver-blue color that is characteristic of the disease. The change in skin pigmentation itself can lead to misdiagnosis. Argyria often is mistaken for cyanosis or cyanotic heart disease,¹⁰ methemoglobinemia, metastatic melanoma, melanuria, or hematochromatosis.¹⁵ The use of antimalarial drugs also may cause a condition that mimics argyria. The diseases to be included in differential diagnosis of argyria are listed in Table 3.

Levels of silver in the blood can be monitored and will provide a sure sign of the disease long before the skin becomes discolored. Ocular pigmentation, which frequently is present in argyria, occurs earlier than changes in skin pigmentation.⁵ On the conjunctiva, pigmentary changes are seen at the caruncle and semilunar folds. Corneal pigmentation is exhibited by the appearance of a pigmented inner ring adjacent to the limbus. Patients may complain of decreased night vision. The ankles also may exhibit early signs of argyria,¹⁸ and the discoloration is also found on the proximal half of the

TABLE 1. OCCUPATIONS THAT ARE AT HIGH RISK FOR ARGYRIA.

Occupation	Silver compounds utilized in occupation
Copy machine operator	p-methyaminophenol sulfate-hydroquinone
Furnaceman in melting plants	Crude ore refinement
Manufacturing	Silver oxide-zinc for making batteries
Mining	
Photographic processing and developing	Silver halides, nitrates, and thiosulfates
Printing (pressman and camera operators, typesetters)	p-methyaminophenol sulfate-hydroquinone Silver halides, nitrates, and thiosulfates
Silversmiths and jewelers	

fingerprints.¹⁷ If the argyria is occupationally related, the changes in the skin color may be limited to exposed areas on the body. Changes in pigmentation are most evident on parts of the body that are exposed to the sun. The discolorations of argyria may result from silver stimulating the activity of melanocytes as well as from the deposition of silver in the dermis of the skin.^{3,6}

The effects of exposure to silver may not be immediate. Even if there is no exposure to silver for years, the condition may suddenly become worse through exposure to the sun. That is probably the case in the patient we are presenting.

Report of case

An 81-year-old woman was brought into the emergency room after an accident with a nursing home bedpan resulted in a contusion in the area of her right kidney. The patient also complained of arthritis and sinusitis. Another reason that the nursing home representative gave for transferring this patient to the hospital was that "her color was getting worse." The medical history was incomplete because the patient suffered from senile dementia. She was disoriented as to time and place and otherwise confused, and she later proved to be incontinent of urine.

On physical examination, the patient was noted to have blue lacunae, silver facies, and silver nasal mucosa, and it initially was thought that she was cyanotic. Her vital signs were as follows: blood pressure, 124/66 mm. Hg; pulse rate, 84 beats/minute; respiratory rate, 28/min.; and temperature, 101.6 F. Her lungs were clear on auscultation, and there were no grossly abnormal cardiopulmonary findings. Urine cultures were negative with lead levels in the normal range. No silver showed up in the blood. The patient's medical records were obtained, and they revealed that some 40 years earlier she had used Argyrol nasal packings once a week for a period of 2 years as sinusitis therapy. During that time, her skin color had changed, and she had been diagnosed as having argyria.

There had not been much improvement in the skin color since then, nor had it worsened.

The diagnosis of argyria was made the morning after admission when the differential diagnosis of silver blue skin was reviewed and the initial discoloration noted. The prior history of argyria use was revealed in the medical records. The patient's skin color was different than that described as having resulted from her initial exposure of silver. The medical records did state that the use of argyria was discontinued because of the patient's subjective feeling of skin discoloration. No silver was detected in the blood during the present hospitalization. The appearance of the patient's mucosal surfaces, especially the nasal mucosa, was light pink with areas of bluish black discoloration.

Three days after admission, the patient began to show seizure activity of the grand mal type. Computed tomographic (CT) scanning of the brain revealed ill-defined lucencies in both the left and right parietal areas, with no associated masses. There also was evidence of mild atrophy, which was both central and cortical. Both hemispheres were well perfused. The electroencephalogram (EEG) was abnormal with asymmetry of the background activity.

Punch biopsy of the left nasolabial fold was performed, and hematoxylin/eosin-stained sections revealed fine granular particles in and about adnexal structures.

The patient was given Dilantin, which controlled the seizures. The patient's diet was modified so that she received all of the essential nutrients, and was discharged after her Dilantin levels were stabilized. The staff at the nursing home where the patient was living were notified of the patient's sensitivity to the sun, along with the expected results to sun exposure.¹⁹

Case discussion

The patient's 2 years of Argyrol nasal packings most probably was the cause of her argyria. Her silver-blue color caused some confusion at first, and she was misdiagnosed as being cyanotic. Her color was one of the reasons that she was brought into the hospital. She had just moved into a new nursing home, and the staff there were not aware of her condition. Therefore, she may have been taken out in the sun more often than before, which could have led to her discoloration becoming more pronounced.

It is important to note that the CT scans revealed ill-defined lucencies of unknown origin, and that the patient had an abnormal EEG pattern. No other physical findings were associated with the patient's argyria. These disorders could have been caused by the silver that was absorbed through the nasal mucosa. There would be no need for the silver to cross the blood brain barrier after entering the body via this method. Parietal lobe lesions are consistent with personality disorders, including senile dementia. The fact that the lesions were bilateral seems significant. There are other cases in which

metals have been reported to deposit in a certain area of the brain. One such example would be Wilson's disease, in which copper causes large cavitations in the basal ganglion of the brain bilaterally.¹⁷

Comments

The effects of argyria usually are assumed to be primarily cosmetic. There is a definite increase in melanin pigmentation, which is stimulated by the deposition of silver. In localized argyria, the highest concentrations are to be found around the basal exocrine sweat glands¹⁹ and around hair follicles.²⁰ The deposits are round or oval bodies in localized argyria; occasionally the silver will form concentric rings.¹⁹ Silver is seen throughout the dermis, but it is almost never found in the epidermis. There are aggregations of phagolysosomes in the cell, and silver is found within the mitochondria.¹⁹ When toxic doses of silver are introduced into the body, there are definite cidal effects on the mitochondria.¹⁸ Silver also is deposited around basement membranes and blood vessels, and greyish-blue discoloration is evident on the larynx, gastrointestinal tract, peritoneum, kidneys, testicles, and liver. There also are definite accumulations of silver in connective tissue; these are seen most frequently in patients suffering from senile elastosis.¹⁹

For the most part, the effects of silver on certain physiologic responses generally have not been determined. Silver has been implicated as a cause of decreased night vision,⁴ a cause of mild chronic bronchitis, a possible cause of idiopathic thrombocytopenia, an inhibitor of enzyme activity, and a nephrotoxin.⁸ One study⁸ demonstrated a definite correlation between exposure to silver salts (silver nitrate or silver oxide) and abdominal pain. This pain, which was described as "burning in quality," was relieved with the use of antacids.

There still is no effective treatment for argyria. It is known that exposure to the sun will exacerbate the condition by a process similar to the developing of film. Although the patient discussed in this article abstained from silver compounds for 40 years, there was no appreciable improvement/worsening in her skin color until she changed her lifestyle to one that possibly included increased exposure to the sun.

There have been some anecdotal reports on the improvement of the skin color of patients suffering from argyria. It is not clear whether the beneficial effect was accomplished by removal of the silver or by bleaching of the melanin. The treatment that was most often presented was intradermal injections of potassium ferricyanide-thiosulfate sodium.

TABLE 2. SILVER-CONTAINING THERAPEUTIC COMPOUNDS THAT MAY CAUSE IATROGENIC ARGYRIA.

Use	Therapeutic agents
Antibacterial cleansing	Silver nitrate ointments
Antismoking aid	Silver acetate and ammonium chloride lozenges
Aphthae treatment	Silver nitrate sticks
Burn therapy	Silver sulfadiazine, silver sulfacetamide
Bleeding control (especially gingival bleeding caused by dentures)	Silver nitrate in topical drops
Dental caries filling	Silver amalgam
Folk remedies for chronic laryngitis, gastric discomfort, nervous system disorders, epilepsy, tabes dorsalis, and chorea minor	Silver salts Silver colloids Argento-mercapto-3 hydroxy 2-propane sodium sulfonate m-acetyl amino p hydroxy phenyl sodium arsenate
Indigestion alleviation	Silver-containing antacids
Ophthalmia prophylaxis in neonates	Silver nitrate drops
Perinatal prophylaxis for gonorrhea	Silver nitrate drops
Sinusitis therapy	Silver protein nasal packings
Suturing	Silver sutures (used experimentally)
Wound treatment	Silver Sulfadiazine Mafenide Sulfasalazine Silver sulfacetamide

TABLE 3. DIFFERENTIAL DIAGNOSIS FOR ARGYRIA.

Addison's disease
Cyanosis
Cyanotic heart disease
Drug-induced pigmentations (antimalarial agents - Atabrine, amodiaquine hydrochloride, chloroquine, phenothalein)
Melanuria
Metastatic melanoma (melanosis)
Methemoglobinemia
Pigmentation from heavy metals
Chrysiasis (gold)
Hematochromatosis (hemosiderin and melanin)
Hydrargyrosis (mercury)
Onchonosis (hemogentisic acid)
Wilson's disease (copper)
Polycythemia
<i>Pseudomonas paronychia</i>
<i>Pseudomonas pyocyanea</i>

Unfortunately, this photographic reducing solution became better known for its ability to produce pain than for its effects on the silver deposits.¹⁵ Other agents include potassium iodide and methenamine (Callargol).⁶ No appreciable success has been obtained with any treatment.

Summary

Although argyria is not the first thing that you

think of when a person presents with a bluish discoloration, it must be in the differential. A thorough occupational history is needed as well as a history of medications taken in order to suggest argyria.

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