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A Brief Review on "Argyria Disease

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ABSTRACT

Argyria defined the different cosmetic alteration that can develop if enough silver particle deposit in specific tissue, typically in the skin its ranging localized dark-blue mucules to generalized slate gray/bluish tinge systemic absorption. In these work aim is fully review the state of the art regarding etiology, epidermiology, pathophysiology, histology, sign and symptoms, evaluation, treatment and differential diagnosis of argyria. Argyria has been diagnosed in wide range ages and sexes and varied ethicities.

Keywords: Argyria, pigmentation, silver, discoloration.

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INTRODUCTION

Argyria is a rare condition it occurs when the human body is intake or contact with excessive amount of silver. Because of silver is not absorbed by normal skin, Argyria is caused by absorption of silver via implantation or ingestion from medical instrument. On a daily basis the people come into contact with vary small amount of silver. Silver is present in drinking water, food and even it is present in air which we breathe. [1] The product which contain high amount of silver surpass the body's renal, its leading to silver molecules being deposited in skin and its appendages, mucasae and internal organs (likes the kidney, eye, bone marrow, spleen and central nervous system) and it is acquire a blue-gray pigmentation.[2]

Now overexposure of occupational or iatrogenic silver is very rare, but some cases of Argyria related to the ingestion of silver compounds as folk remedies are still present. Argyria is harmless and has a benign course, but neurotoxicity and myopathy have been associated with a few cases of Argyria. [3] Silver dates back is use as a medicine from beginning of medical history. It is mainly use as an antibacterial and antifungal agent in chronic wound case product, certain textiles, medical devices and calls for a reappraisal of one of its potential side effects. The required amount of silver is absorbed to cause generalized Argyria pigmentation is unknown. There are several different types of exposure (Accidental, occupation, environment and therapeutic), routes of administration (oral, percutaneous and intranasal). According to some authors, skin pigmentation not only caused by silver deposition (in sulfite and selenite form) in the dermis area of skin but also by stimulation of melanine synthesis.[4]

The normal concentration of silver in human body is <2.5 mcg/L absorbed silver gets metabolized to silver ion and bind to protein like macroglobulins and albumin.[5]

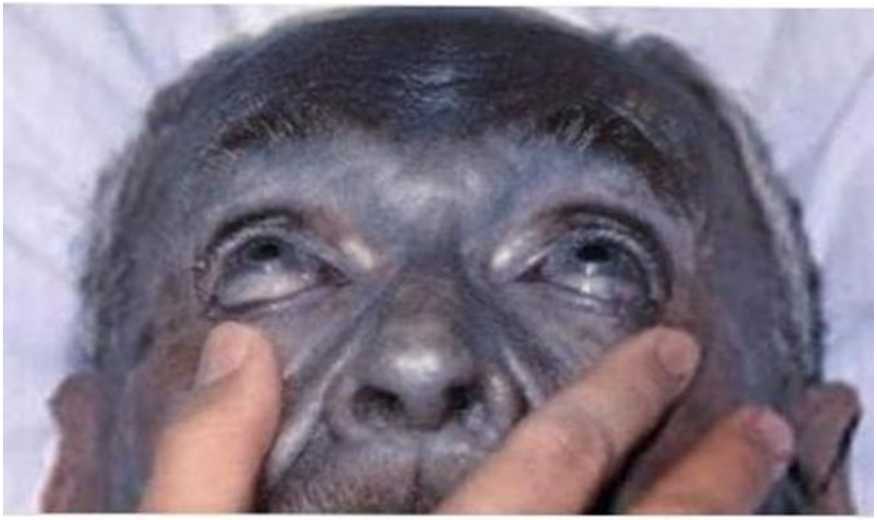

Figure 1: Argyria (https://images.app.goo.gl/AZvSzXcpwVWVAsSc9)

History

Since at least the mid-19th century, doctors have known that the some area of the skin and other body tissues to turn into grey or blue-grey due to silver or silver compounds. Argyria is mainly occurring in the people whose are contact with silver for long time or the consumption of medicine which contain silver. The people who work in the factories that manufacturing silver products, due to the breathe they intake silver or its compounds. In the past the some of the workers become argyric. Is treat a variety of diseases the colloidal silver a liquid suspension of microscopic silver particle, was also used as an internal medication.[6]

The term *Argyria* was first use by Funchs in 1840. In the middle age silver nitrate was used as medicine for treatment of nervous system disorder such as epilepsy and tubes dorsalis. After observing Dr. Halstead of Johns Hopkins University apply silver foil and gauze to wounds to prevent infection in 1897. Silver popularly used as an anti-infective. In the pre antibiotic era silver was used in nose drops in common cold, for treatment if syphilis (NeoSilvol, a silver arsphenamaine) and in sinusitis. Silver- sulfadiazine most frequently used topical agent for burn treatment. It was formulated by substituting a portion of the sulfonamide with an atom of silver in 1967. [10]

Chemistry and History of Silver

Silver derives from the Anglo-Saxon “Seofor” and “Siolfur” , and it is found in solid form at room temperature, it is a chemical element, it is classified as a transitional metal in periodic table period 5 and group 11. The atomic number is 47. Symbol of silver is a (Ag), which derived from Latin word *argentum.* It is a rare element. It is naturally found as a soft “ Silver” coloured metal in its pure form, but it is mostly found in its typical oxidation state (+1) in environment with other ions or molecules such as sulfide, chloride and nitrate, which give colour ranging to compound from dark-grey/ black to powder white. Silver has highest thermal conductivity as well as electrical conductivity and having lowest resistivity to resist electrical and thermal conductivity.

Soluble inorganic silver salt are strongly bactericidal (e.g. Silver, nitrate and silver sulfide) and particularly silver nitrate (1%) it use to prevent gonococcal opthalmitis in newborns. Silver Sulfadiazine slowly releases in patient with second and third degree burn wounds. Silver has important value since ancient times; it is separated from lead as early as 4000 BC. Silver metal is used for silverware, electronic equipment, jewelry and dental filling. For the drinking water disinfection world health organization permissible level is reported to be 0.1 mg Ag/L. Recent application of silver is in nanoparticles (AgNP), materials with sizes between 1 to 15,000 atoms of silver. Because of their antimicrobial activity.

Sliver nanoparticle are used in disinfectants, medical devices, textile, water treatment, appliances.[7]

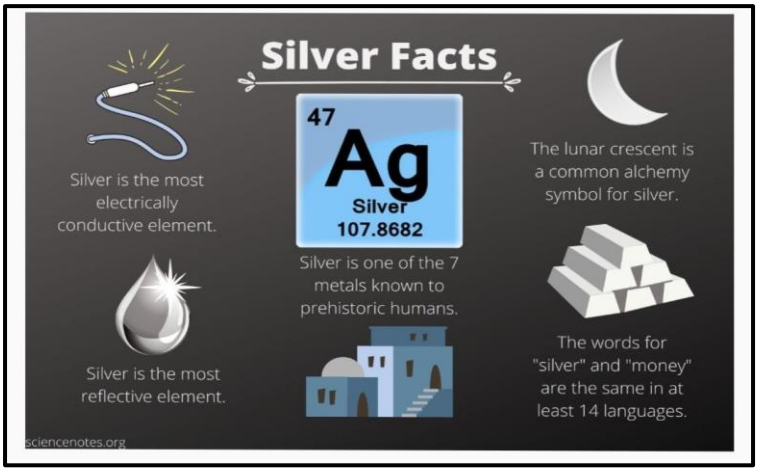

Figure 2: Silver Facts (https://images.app.goo.gl/rhes2ZeARHWg8KQA)

ETIOLOGY

The most common causes of argyria are secondary to exposures in the medicinal use or workplace. Occupational argyria is found in specific area of body. Often transdermal, inhaled, and transmucousal tends to be localized area of body. For example, the finger of jewelry polisher. Ocular argyrosis in silversmiths due to the deposition of silver in the cornea.

It have been reported in some cases. In modern-era the medicinal exposure has become much less common since the antimicrobial properties of silver are unavailing compared to nowadays antibiotics.

Medical uses that are approved by the FDA are given below

- Opthalmic silver nitrate for gonorrheal ophthalmia neonatorum.
- Cutaneous silver nitrate for mucosal cautery.
- Silver impregnated catheters and endotrached tubes as an antimicrobial adjunct.
- Cutaneous silver sulfadiazine for wounds secondary to second and third-degree burns.
- Mucocutaneous silver acetate for smoking cessation because of its foul, metallic taste when combined with smoke.

The hygiene capacities of silver show resulted in addition of silver in products like hair dye, bandaids, contact lenses, breast pump assemblies and toothpaste. An immune system promoter it is advertised and also it is available of grocery stores, pharmacies as well as

online.7

EPIDEMIOLOGY

Argyria typically seen in the people who consume colloidal silver or form of alternative medicine. Argyria affected individual of all age groups or genders without any specific predilection.[8]

Argyria has, decreased the amount of patient in the last years. Because of the uses of the silver compound in the medicines or medical prothesis better controlled and also in the exposure in the silver industry. Of the cases registered, the major part is constituted by male patients over the age of 50; it could be seem as depending on a social aspect. For instance, worker in factory. It is seen in the older people because it obtain when patient are contact over the period of years.[9]

Pathophysiology

In electrophilic compound the covalent adduct formation is common because they react with nucleophilic atoms in nucleic acids and protein. In general the strong electrophiles react with strong nucleophiles (high charge to-radius ration in both) whereas the soft or less strong electrophiles are prefer react with soft nucleophiles (low charge to-radius ration in both), such as oxygen in nuclic acids. Metal ions as silver or mercury are soft electrophiles they are react with soft nucleophiles, like thiol groups, such as cysteineabunadant collagen fibers and proteoglycans in the extracellular matrix and the metallothioneins intracellular which synthesis is induced after cellular silver intake.

In the absence of light as occurs in the gastro intenstinal tract, argyric dicoloration may be due to the role of tissue enzymes or other redox system in the conversion of silver to its elemental form. There is evidence of silver found intracellular, lying in the cytoplasm or bound to lysosome- like structures inside histiocytes and fibroblasts, suggesting a cellular uptake role in its clean up, but not only way near an extent the enables pigmentation resolution therefore, silver is clearly found mainly in extracellular locations.

Silver gains access to the dermis or other tissues, either carried by the blood steam or localized, it is deposited like a predictable pattern, as shown by ultrastructural studies and histopathological studies. The macroscopically appearance of the dicoloration is also influences on the outermost skin layer. Since it reflects light in the blue or violet spectrum more than in longer wavelength, at clinical evaluation the argyria colours are usually perceived as blue or grey. In anatomic place colour may be less intense, where *stratum corneum* in thicker. The patient which having similar conuntration of silver particles in dermal tissue it have less pigment appearance on hand or palm than the dorsa.

Regarding azure lunula, the pathophysiology explaining the prevalence of discoloration in the lunula in comparison to nail beds is not yet clarified. What is known is that the nail plate is translucent, allowing the visualization of the underlying nail bed. It also grows thicker distally, being thinner in the lunula. With nail formation, cells move forward from the lunula (keratogenous zone), suffering fragmentation until they are predominantly a nucleated, eosinophilic, and arranged

in very compact sheets. These two factors (nail plate thickness variation and changes in keratinocytes along the nail plate) might play a role in the colour disposition found in argyric nails (azure lunula), as well as a richer vascularization toward the nail matrix when compared to the nail mid bed.[7]

In the human body the natural silver is present in small amount, these silver is increase with age in the body. The increase the amount of silver, the metal reduction and photo activation in body produce bluish gray decolouration of skin in the exposure areas.[8]

TYPE OF ARGYRIA

There are three subtype of argyria which are following:-

- Generalized Argyria
- Localized Argyria
- Argyrosis

Generalized Argyria:-

In generalized argyria, patient were most commonly present with gradually aggravating face and neck discoloration with a history of oral but also occupational aerosolized exposure to silver containing product. Different minimal amount of elemental silver cumulative oral intake able to produce generalized argyria have been suggested ranging from 2 to 30g but such values provide incomplete information unpaired with a time window. Another possible early sign of generalized argyria is acquired pigmentation of oral mucosa unlike amalgam tattoos a diffuse gray/blue ting will be seen. [7]

This type of argyria is produce to systemic exposure of silver by its uptake by dermis and it leading to a grey/blue selfish or metallic diffuse to the skin. This colour difference becomes evident predominantly is seen exposed areas. Azure lunula is a subtype in which there will be a bluish discoloration of the lunula of fingernails. [8]

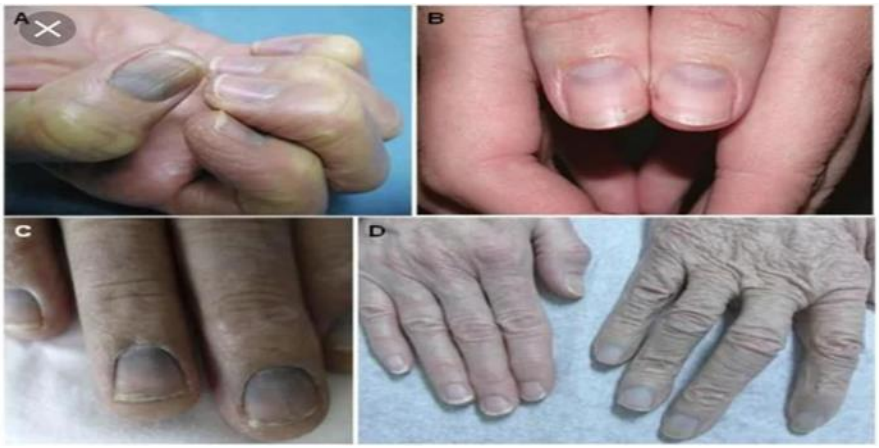

Figure 3: Azure Lunula [7]

Based on a bio-spectrometric analysis of ten of the seventy cases of generalized argyria, Gaul and Staud were able to show that the degree of discoloration of patients directly correlated with the amount of silver present.[10]

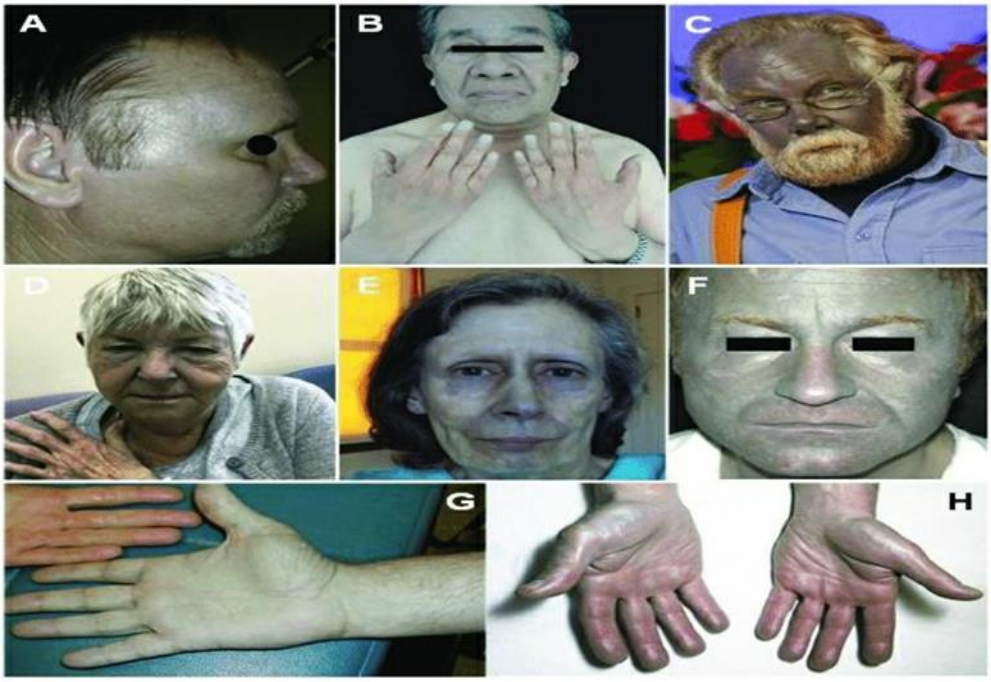

Figure 4: - Generalized Argyria 7

Localized Argyria

The type of argyria is less commonly seen, these is occur when the silver deposition by the absorption into skin incision or percutaneous via sweet gland pores. The colour which form on skin in localized argyria, it is tends tube darker, sometimes almost black. These type of argyria found in the patient who's most commonly contact with the silver containing objects like cream, solution etc. It is occur in the hands and forearms of silver handling workers.

Besides silver, it is important to highlight the dental amalgam cloud also present silver, zinc, copper and tin which may also have a role in the development of amalgam tattoos. Other less common form of localized argyria reported is in the tracheal and bronchial mucosa, vagina, penis, urinary tract and nasal. [7]

Amalgam tattoo it is the most common subtype of localized argyria. It is usually found in mouth it occurs when the patient goes under the dentistry procedure. In this process silver contained dental amalgam is impregnation into oral mucosa. It is characterized by a flat, dark-blue mucosal lesion near a restored tooth. [8]

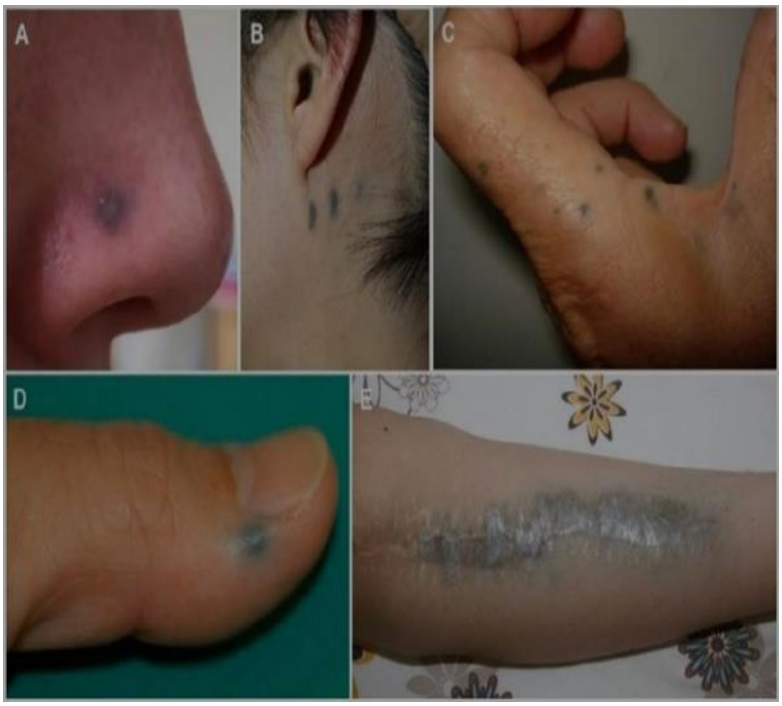

Figure 5: Localized Argyria[7]

Argyrosis

Argyrosis is particular argyric manifestation evidence by the osculer silver deposition that occur in generalized argyria, but also as a localized argyria form. It is mostly found in the bulbar, cornea and palpebral conjunctivae and lacrimal caruncle. [7]

This is also one of the subtypes of argyria. This is occurring due to deposition of silver in the eye. The lesion has a predilection for the corneal desienet membrane and appear small, darker lesions with greenish and brownish tones. [8]

It is associated with a deposition of silver salts. These silver salts can either be a from external sources, such as silver containing cosmetic makeup eye drops and through systemic silver deposition. Most structure of eye is involved in other than the optic, lens, vitrous, nerve and retina. There have been some reports related to ocular argyrosis developing from occupational exposure of silver nitrate in an industrial plant and corneal argyrosis from an explosion injury. [10]

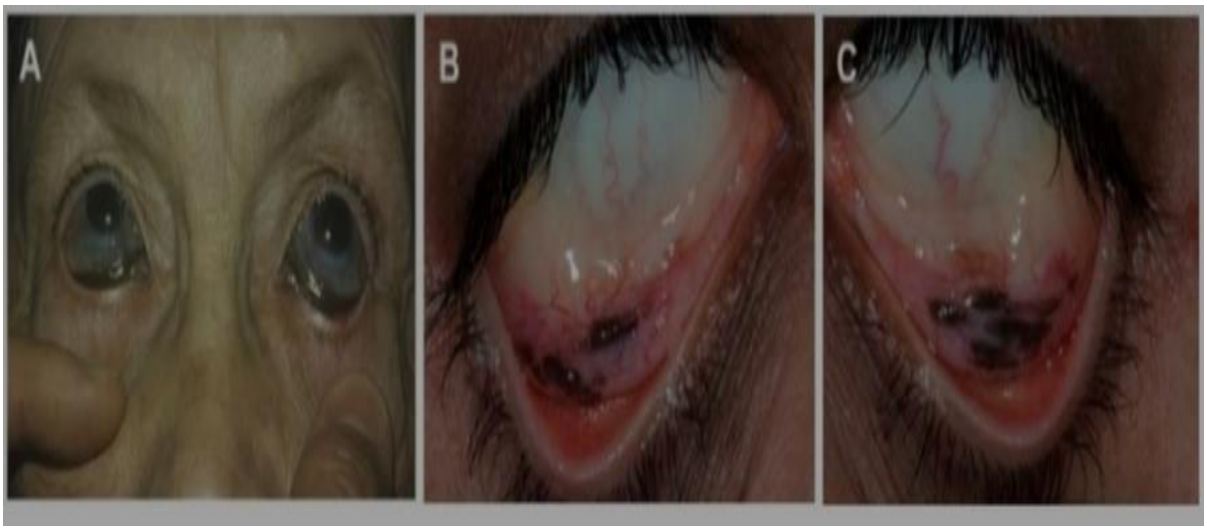

Figure 7: Oscular Argyrosis [7]

Histology

Histological examination of argyria disease is carried out by the skin biopsy in patient suspected to have argyria will reveal numerous, brown, tiny or black granules which are deposited in a linear distribution along the basement membrane of eccrine glands. In the elastic and collagen fibres within the papillary dermis there are also the granule are deposits, under the microscopic the deposits silver can be confirmed by using hematoxylin and eosin staining. Histological, argyria can be mistaken for melanoma. Despite that, it is not a precancerous or cancerous condition. The epidermis is spared, which is a characteristic that may be used to help distinguish argyria from other pigmentation disorders. [8]

The distribution of silver is due to the relatively vascular networks in this region. Silver granules are absent in the epidermis. However, due to these the melanisation of the epidermis is increase and dermal melanophages is seen. This absence of any silver deposits in the epithelium in generalized argyria is documental in many studies. In the nerves, capillary walls, fibroblast, elastic fibres, perifollicular sheaths and macrophages the silver particles in high concentration are demonstrated.

The brilliantly refractive granules that are very easy to seen against a dark background in a dark field microscope. This technique is especially use when the silver particles are not seen under the light microscopy a sample of patient which has argyria. The conformation of silver granules which are seen along with the basal lamina of the epidermis and blood vessels by xray microanalysis. [10]

Sign and Symptom Related Argyria

Sign and symptoms derived from silver exposure are usually absent in cosmetic changes. Silver has low toxicity in humans. The deposited silver is not harmful to the surrounding tissue. The

visual symptoms are reported in patient with ocular argyria. Most commonly nyctalopia and presented with concomitant comorbidilies, such as glaucoma and diabetic retinopathy as well as posterior eye segment changes and cataract, but in which silver deposition without direct like to the itself.

In several tissues the settled silver is found and is raised to possible symmetric toxic effects. Regarding the kidney, decreasing in the glomerular filtration rate has been suggested by the reporting of nephrotic syndrome, membranous nephropathy and acute and chronic renal failure but a causal relationship could not be defined. In a 47 year old woman development of an anti-neutrophil cytoplasmic antibiotic (ANCA) negative paucimmune glomerulonepthritis with a T cell lymphoma reported, the deposition of silver in glomerular basement membranes through seemingly innocuos it may be patient with auto immunity disorder trigger for leucocyte mediated aggression.

Most common symptoms of argyria is associated with the silver dust and compound absorbed and stay in long time in body and is exposed by sunlight.

- Slate gray or blue tint discoloration of the skin
- Black or blue discoloration
- Hyperpigmentation that develops on the nail bed of the fingers and toes
- Hyperpigmentation of the mucous membrane and whites of the eyes (conjunctiva)
- Discoloration of the in areas of the body exposed to sunlight including the face, nose, forehead, hands, chest and back
- Slate gray or blue internal organs that are revealed during surgery or autopsies, usually involving the spleen and liver.[11]

Evaluation

Argyria is considered a diagnosis of exclusion, and most cases are diagnosed after a thorough history and physical exam. The gold standard for diagnosis is a skin biopsy of the affected region of the body. As discussed in the histopathology section, a biopsy of an affected area of skin will show brown or black granules deposited along the basement membrane, surrounding eccrine glands and hair follicles. Energy-Dispersive X-ray Spectroscopy (EDXS) is the non-invasive gold standard technique. Dermatoscopy for localized argyrosis and slitlamp bio-microscopy for argyrosis are other methods used for the diagnosis.[8]

Treatment

Commonly presented as hyperpigmentation over sun exposed areas. Though not yet understood reduction of complex silver proteins to elemental silver forms by photo activation stimulate

melanogenesis. No pathological changes or inflammatory reaction visible on histology from silver deposition diagnosed is by measurement of 24 h urine concentration of silver and serum silver concentration. Normal serum silver concentration is 1 mcg/l or below and 24 h urine concentration is 2 mcg/l or below in a patient without history of exposure to silver ingestion. Skin biopsy shows light microscopy black brown globules that are adherent to dermal elastic fibres, blood vessels, basement membrane, hair follicles, and sweat glands. Dark field microscopy shows refractile particles. Electron microscopy with energy dispersive radiography shows silver deposits over basement membrane. Antioxidants such as selenium and vitamin E supplementation and sunscreen applications are effective in reducing further
pigmentation.[5]

The few studies have been documented of removal of coloration but it found to be without appreciable success: depigmenting creams, chelation therapy with different drugs such as 2,3dimercapto-1-propanol (i.e., dimercaprol), 2,3-dimercapto-1-propanesulfonic acid (DMPS), sodium thiosulfate, potassium ferrocyanide, potassium iodide, ethylenediaminetetraacetic acid (EDTA), methenamine and D-penicillamine/N-acetyl-DL-penicillamine, hydroquinone and dermal abrasion all proved ineffective in removing silver deposits from the body. Some of these chelating agents have been reported to lighten the pigmentation in small skin areas after intradermal injection, particularly sodium thiosulfate and potassium ferrocyanide, but results are inconsistent, and their application to larger areas would be quite incommodious and burdensome, with the risks associated far outweighing the unlikely benefit. [7]

Both Q-Switched 1064 nanometres Neodymium-doped Yttrium Aluminum Garnet Laser (QS 1064 nm Nd:YAG laser) and Q-Switched Picosecond 755 nanometres Alexandrite Laser (Q-S P 755 nm Alexandrite Laser) have been reported to yield satisfactory results. The former, ranging from a fluency of 0.7 to 8 J/cm2, a pulse duration of 5to 50 ns, a of 5 to 10 Hz, and a spot size of 2 to 8 mm, produced immediate results, restoring the expected skin coloration for each subject in the targeted areas. As with the latter, at least similar efficacy was obtained within reported values of 0.71 to 2.83 J/cm2 regarding fluency, 0.75 ns regarding pulse duration, 3 to 5.5 mm regarding spot size, and 10 Hz regarding frequency. The persistence of restored skin coloration has been reported up to one year after treatment.

Otherwise, there has been one report of argyria pigmentation recurrence 11 months after Q-S 1064 nm Nd: YAG laser treatment, despite the patient stating discontinuation of silver exposure, use of facial and body sunscreen with a sun protection factor superior or equal to
30, and resort to physical sun-protective barriers.[7, 8]

Treatment of Amalgam tattoo:

The treatment of amalgam tattoo has also been an object of attention. The operator should be ensuring that the area of silver containing root canal sealer are properly clean-up and removed to prevent the lesion onset, especially when the procedure required soft tissue flap reflection. After LA develops, if the lesion is cosmetically unacceptable, surgical excision and transplantation of oral mucosal tissue/free gingival grafting, as well as sub epithelial connective tissue grafts, have been reported, with heterogeneous results (even with LA resolution, the final aesthetic outcome might not be optimal). Regarding the secondary prevention, before the grafting the affected tissue, to remove the amalgam restoration and reduce the amount of depressed silver particles by periradicular surgery. [7]

Treatment of Argyrosis:

For the oscular argyrosis, the patient is treated by Q-switched neodymium-dropped yttrium aluminum garnet (Nd:YAG) laser. The argyrotic deposits antirior to the iridotomy site is clear by the each laser of Q-switched neodymium-dropped yttrium aluminium garnet (Nd:YAG), the procedure was also performed in the contralateral eye as a preventive measure. The cleared cornea area remained unchanged for at least

eight months. [7]

Argyria is considered as a permanent, irreversible skin condition. On this disease many treatments have been attempted but the treatments are not got success. Among these, chelation has been notable result dermabrasion and hydroquinone has been trailed. Recently, some report reported in the literature. After the laser treatment there have temporary improvement of cosmesis. Q-switched neodyminum- dropped yttrium aluminium garnet (Nd:YAG) laser therapy is use to removal of very dark pigmented tattoos and also use to reduce the grey and blue pigmentation in the patient with argyria disease. The study of the Qswitched neodyminum- droped yttrium aluminium garnet (Nd:YAG) laser therapy found that the fluency of these particular laser therapy is too harmful for argyria, and it induced pinpoint bleeding and marked pain.[8]

Toxic kinetics of Silver

Silver is primarily absorbed by the gastrointestinal tract, lung, and skin. Metallic silver and insoluble silver compounds are not readily absorbed and pose a minimal health risk, unlike particulate or colloidal silver, whose toxicity comes from released ionic particles. Inhalation of aerosolized particles, typically occurring in the occupational setting, is also a relevant pathway for silver absorption, but the toxicokinetic properties of this process remain even more uncharacterized. There has been some consensus around 0.01 mg/m3 as the threshold limit value

for daily silver occupational exposure, but a lower limit of 0.1 mg/m3 for metallic silver is becoming more common, as it shows less propensity to cause argyria than its ionic, more soluble and absorbable counterpart. Silver is transported in the bloodstream as a colloid, in its ionic form (Ag+), stabilized by complexing with proteins, mainly albumin but also globulins. It is widely distributed to most tissues, such as muscle, cerebellum, spleen, duodenum, heart, lung, liver, and kidney. It is not clear whether silver crosses the blood-brain barrier, although several studies indicate accumulation in specific areas of the brain. Indeed, silver deposition has been documented in the blood-brain barrier (vascular endothelium and astrocytes), the blood-cerebrospinal fluid barrier (choroid plexus), and the cerebrospinal fluid itself. Moreover, Landas et al. reported a *postmortem* evaluation with silver deposition in circumventricular organs and hypothalamic nuclei, suggesting silver's eventual passage to the central nervous system. Nevertheless, the state of the art is far from being clarified.

The primary routes of exposure for AgNP include excretion occurring predominantly in the bile but also through the urinary system in a much lesser amount. Indeed, biliary excretion is important in the homeostasis of several metals, notably copper, manganese, cadmium,
selenium, gold, silver, and arsenic. [7]

Consumption of large dose of colloidal silver can result in coma, pleura edema, and hemolysis. Colloidal silver may be associate with agranulocytosis and is also toxic to the bone marrow. The toxic effect of inorganic silver ingested orally in large doses are very similar to any corrosive solution such ingestion can result in vomiting, leading to abdominal pain, diarrhoea and burning of the throat and epigastrium. The patient goes into shock. The single lethal dose of silver nitrate has been estimated to be 10gm. Silver salts are more toxic than silver proteins or colloidal silver. The EPA publishes an oral reference dose (RfD) that is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. This dose is expressed in units of micrograms per kg per day and is an estimate of the maximum amount of daily silver exposure to the human population that is not associated with any appreciable deleterious effects over a lifetime. Current RfD for oral silver exposure is 5 micrograms per kg per day. When consumed in relatively smaller quantities, no pathologic changes or inflammatory reactions other than argyria have been shown to result from silver deposition. However, if silver is administered in high doses, whether orally or intravenously, there is ample evidence of adverse effects including death. On the basis of animal experiments, many authors in the late nineteenth century determined that intravenous administration of inorganic silver has the most significant impact on the central nervous system

(manifested as weakness and rigidity of the legs, loss of voluntary movements) and on the cardiac conduction system (abnormal conduction).loss of voluntary movements) and on the cardiac conduction system (abnormal conduction). [10]

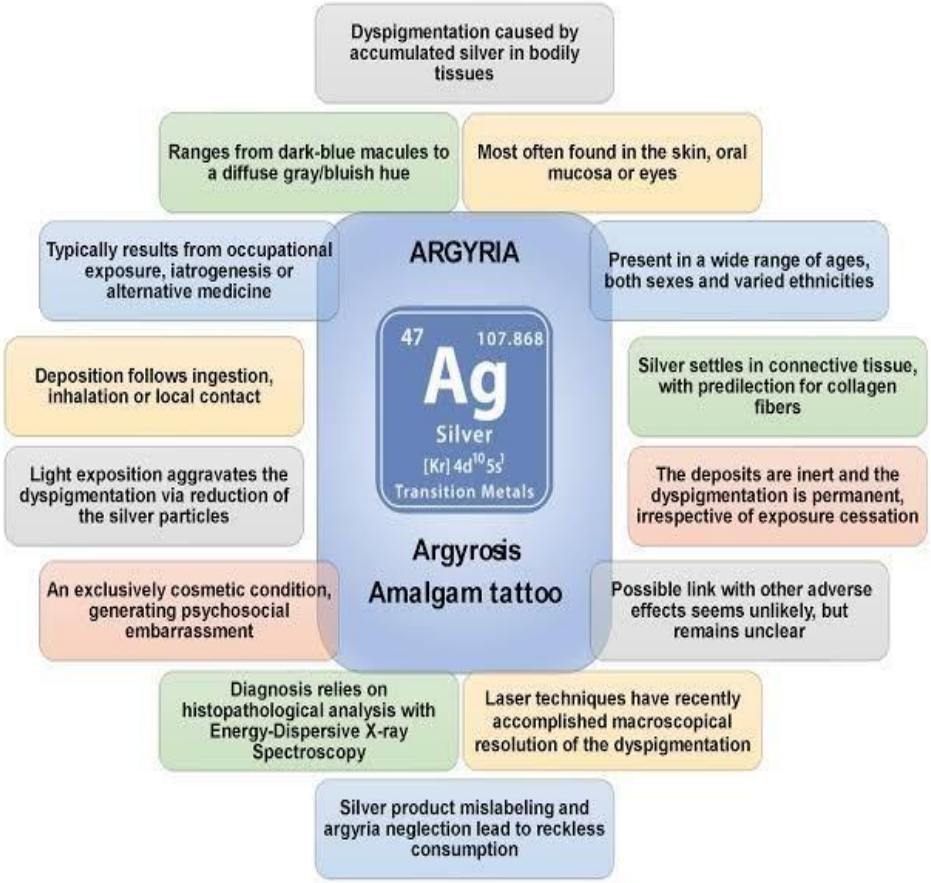

Figure 10: Major characteristics of different forms of argyria.

Diagnosis of Argyria

Type of argyria is confirmed by differential pigmented lesion. Any of these finding might correspond to argyria: localized dark-blue lesions, eye gray/brown/dark spots, the characteristic nail changes seen in azure lunula, and a slate-gray/ bluish changes of complexion in sun exposed areas. Silver product exposition, as in oral silver consumption in a generalized argyria-suitable patient, a previous dental restoration in a patient presenting with amalgam tattoos, or acupuncture history in a patient with dispersing cutaneous localized argyria lesions, can be highly indicative of argyria. [7]

The diagnosis of argyria is clinical. The biopsy of the affected skin of the argyria patient to confirm the diagnosis. The histological appearance of this condition manifests as tiny granules as previously stated, of a brownish colour and measuring approximately 1mm, in extracellular spaces and especially in the adventitia of eccrine glands. [9]

There is differential diagnosis

- Cyanosis
- Hemochromatosis
- Methemolgobinemia
- Methylene blue poisoning
- Melanoma
- Ochronosis
- Chrysiasis
- Amiodarone, minocycline or prenothiazines use.

Table 1: Main differential diagnosis for argyria. [7]

Disease	Chemical Substance(s)	Presentation	Histology
Ochronosis		Blue, Black/Blue pigmentation, mainly localized.	Collagen fiber basophilia. Free coarse deposits or intrahistiocytic, perivascular or periadnexal granules.
Alkaptonuria	Unmetabolized Homogentisic acid	Autossomic Recessive Disease.	
Exogenous Ochronosis	Phenol derivatives (e.g. antimalarials)	The pigment distribution depends on administration route. Reversible.	
Hemochroma Tosis	Iron (hemosiderin)	Generalized Hyperpigmentation (blue-grayish pigmentation possible)(photoaggravated). Reversible.	Hypermelanosis of the basal cell layer. Hemosiderin granules within histiocytes and on the basal membrane of sweat glands. Perls +*
Chrysiasis	Gold (e.g. gold salts)	Generalized blue-grey pigmentation (photoaggravated). Irreversible.	Perivascular and intrahistiocytic granules on the intermediate and upper dermis.
Phenotiazines	(e.g. chlorpromazine)	Generalized blue-grey pigmentation (photoaggravated). Reversible.	Intrahistiocytic, perivascular and free superficial granules.
Minocycline		Several patterns. In type II pattern there is bluegrey localized pigmentation on the limbs. Reversible.	Intrahistiocytic and perivascular pigment. Perls +, Fontana-Masson +
Amiodarone		Generalized blue-grey pigmentation (photo aggravated). Reversible.	Perivascular intrahistiocytic pigment on the intermediate dermis. Fontana-Masson +, PAS +, Ziehl-Neelsen + e Sudan black +

* - The "+" sign denotes findings highlighted by the stain mentioned.[4]

Table 2: Overview of major causes of argyria. [7]

Treatment	Causes
Gastrointestinal condition (ingestion of silver containing	Iatrogenic, systemic

colloids/pills)	
Leukoplakia patch (topical application of silver nitrate)	Iatrogenic, topical
Epilespy and other neuropsychiatric conditions (ingestion of silver containing pills)	Iatrogenic, systemic
Alopecia (ingestion of silver containing colloids)	Iatrogenic, systemic
Prophylaxis of gonococcal opthalmia neonatorum (application of silver nitrate collyrium)	Iatrogenic, topical
Syphilis (topical application of silver arsphenamine)	Iatrogenic, topical
Wounds/ulcers/burns/(topical application of silver sulfadiazine cream for asepsis, silver nitrate for chemical cautery/ hemostasis, and use of silver impregnated suture threads/surgical clips)	Iatrogenic, topical and systemic (if bloodstream is reached)
Strabismus surgery (application of silver nitrate collyrium and use of silver impregnated suture threads/surgical clips)	Iatrogenic, topical

Table 3: - Differential diagnosis for other Argyria mimicking pigmentation of skin and other tissues. Generalized argyria, localized Argyria. [7]

Pathological condition of xenobiotic	**Description**
Hemochromatosis	Generalized skin hyperpigmentation (Generalized argyria)
Lead poisoning	Blue line along the gingival margins at the base of the teeth (localized argyria, amalgam tattoo)
Methemoglobinemia/ sulfhemoglobinemia	Generalized skin brownish-blue to gray pigmentation (as in cyanosis) (generalized argyria)
Toxic melanodermatitis	Hyperpigmentation skin lesions (localized and generalized argyria)
Minocycline	Blue staining of teeth or blue-gray skin lesion (generalized argyria)
Chlorpromazine/ phenothiazines	Slate gray-bluish skin discoloration in sun exposed areas (generalized argyria)
Amiodarone	Slate gray-bluish skin discoloration in sun exposed areas (generalized argyria)

Prognosis

Argyria is exacerbated by continued silver ingestion or exposure, and this is due to an accumulative effect. It does not improve after discontinuing exposure. Ultimately, the prognosis is permanent skin discoloration of the areas affected. Although not a life threatening condition, it results in an un-favorable cosmetic outcome. [7]

The prognosis (outlook) is often bleak for individuals who suffer mild to severe cases of argyria. This is because it is often challenging to reverse the effects associated with the condition other than the limited results of laser treatment. However, the condition is not life threatening and has never been associated with any ill effects, reproductive issues, neurological problems, cancer, or another malady. Mild cases involving argyria are easily managed by a competent dermatologist.

However, the patient can develop some complications including persistent bronchitis, loss of coordination, decreased night vision, equilibrium impairment, hemorrhaging, and others. Typically, patients suffer the social defects of the condition because of the cosmetic discoloration of their skin that often generates a harsh emotional toll that directly affects the quality of life. This can extend to anxiety, depression, and apprehension about living a normal life and learning coping skills from a trained counselor or therapist to overcome the social norms associated with skin abnormalities. [11]

CONCLUSION

The entire silver containing product should be labeled with clear warning to prevent to argyria disease, mostly in alternatively health practices. Increase the awareness in public about neurotoxic effects of silver containing products.

Ingestion of chronic Ayurveda drugs containing heavy metals like mercury and silver is one of cause for hyperpigmentation, so we concluded that argyria was a diagnosis made on clinical history and careful examination. Failure to recognize argyria may result in prolonged psycho-social morbidity and unnecessary investigations and treatments.

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