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A curious association of chronic homeopathic arsenic ingestion with nonspecific symptoms in a Swiss teenager

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Summary

Arsenic is a toxicant that has no dose threshold below which exposures are not harmful. Here I report a curious association of chronic homeopathic arsenic ingestion with nonspecific symptoms in a Swiss teenager. For about 4 years she had taken globules of a freely purchasable homeopathic remedy containing inorganic arsenic (iAs), infinitesimally diluted to D6 (average arsenic content per single globule: 0.85 ± 0.08 ng). In the previous 7 months she had taken 20 to 50 globules daily (average 30 ng arsenic daily). She complained of nausea, stomach and abdominal cramps, diarrhoea and flatulence, headache, dizziness, anxiety, difficulty concentrating, insomnia, snoring, leg cramps and fatigue, loss of appetite, increased thirst and sweating, reduced diuresis, weight gain, paleness and coolness of both hands with a furry feeling of the hands, eczema of the hands, arms and legs, conjunctivitis and irregular menstruation. The physical and laboratory examinations showed a body mass index of 30 kg/m^2, acne vulgaris, bilateral spotted leukonychia, eczema of hands, arms and legs, non-pitting oedema of the legs, elevated plasma alkaline phosphatase activity, folate deficiency and severe vitamin D3 insufficiency. The arsenic concentration in her blood was <0.013 µmol/l, and arsenic was undetectable in her scalp hair. The total iAs concentration was 116 nmol/l in the morning urine and 47 nmol/l in the afternoon urine. The urinary arsenic concentration decreased and the patient's complaints improved upon interruption of the arsenic globules, vitamin D3, thiamine and folic acid supplementation, and symptomatic therapy. It is concluded that an avoidable toxicant such as inorganic arsenic, for which no scientific safe dose threshold exists, should be avoided and not be found in over-the-counter medications.

Keywords: *arsenic, inorganic, intoxication, osteoresorptive, homeopathic, Switzerland*

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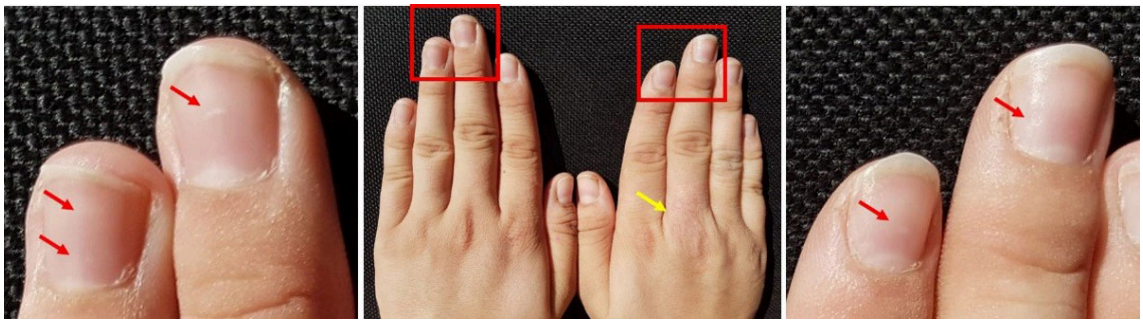
Case report

A 16-year-old Swiss adolescent attended her family doctor's office with complaints of recurrent severe headaches since November 2017. The headache showed no improvement with various analgesics and with physiotherapy. As of March 2018, the headache appeared to be triggered or increased by noise. During the headache attacks, her face felt as if it were swelling. The patient described the pain as a continuous stinging, mostly on the frontal right side of her head but also holocephalic. The headache was so severe that she could not help crying. For years the patient had been overweight, but she had felt as if she was putting on weight during recent months. A nonatopic eczematous dermatitis had been present since childhood, but had worsened since the end of 2017. In addition, she complained of chronic fatigue and disturbed intestinal function with diarrhoea more than five times a day, thin stools after consumption of dairy products, and constipation with flatulence when she was on a lactose-free diet. She had reported stuttering since 2012, though this symptom had remained unchanged in recent years. The laboratory examination from 2 February 2018 showed an unremarkable blood count; glutamate-oxaloacetate transaminase, glutamate-pyruvate transaminase (GPT) and gamma-glutamyltransferase (GGT) activities, as well as creatinine and IgE concentrations were all within the reference range (RR). The alkaline phosphate activity (ALP) was slightly elevated at 124 U/l (RR 35–105 U/l). On 19 March 2018, upon referral to a psychiatrist, the patient was diagnosed with severe tension and anxiety associated with starting a new job and stuttering. The patient is a non-smoker; she denied consuming alcohol or psychotropic drugs.

On 3 May 2018, the patient presented herself for the first time in my office in Sargans, Switzerland. She complained of insomnia, excessive sweating, snoring and fatigue. She felt cut off, unable to concentrate. She had gained 5 to 6 kg within 6 months. For about one and a half years (since about early 2017) she had taken paracetamol for increased abdominal pains and flatulence. The gastrointestinal complaints had started 4 years ago, in 2014, and increased in 2016, in connection with psychosocial stress related to her studies. Since 2014, she had taken globules of some free purchasable, inorganic arsenic-containing Swiss homeopathic "gastrointestinal discomfort globules" daily [1]. Initially, she took such globules from her grandmother, on an irregular basis; however, with increasing gastrointesti-

Figure 1: Bilateral spotted leukonychia (red insets, red arrows) and eczema (yellow arrow) in the patient.



nal complaints, she increased the frequency of globule ingestion and the number of globules ingested each time. From October 2016, she began to take, on average, some 20 globules daily. In the last 7 months she increased the daily doses to 20 to 50 globules daily. The patient reported that she had consumed "a lot of" 15 g bottles of the globules, but she could not remember exactly how many there were. Her mother assured me she had consumed some 12 to 18 bottles in the last 3 to 4 years (one 15 g bottle every 2–3 months). She had taken no other prescription or recreational drug. Physical findings were: weight 76 kg with clothes (estimated naked weight: 75 kg), height 158 cm, body mass index (BMI) 30 kg/m^2. There was acne vulgaris on the face, neck, chest and dorsum and eczematous dermatitis of the hands and arms. Bilateral spotted leukonychia (not the classical traverse leukonychia or Reynolds-Aldrich-Mees' lines) of fingers II and III of the right hand as well as fingers III and IV of the left hand was noted (fig. 1). The blood count was unremarkable. Thyroid stimulating hormone and ferritin were within the reference range. There was a severe vitamin D_3 insufficiency, a serum 25(OH)D concentration of 16 µg/l.

At the follow-up visit on May 17, 2018, she complained of worsening symptoms including stomach cramps, pinching sensation of her stomach, and severe leg cramps. She had a bilateral pretibial pressure dullness and a throbbing dullness of the kidneys. The urine status was unremarkable. Laboratory results at that time included: parathyroid hormone 5.3 pmol/l (RR 1.6–6.9 pmol/l); ALP 129 U/l (35–105 U/l); holotranscobalamin 102.8 pmol/l (> 50 pmol/l); creatinine: 65 µmol/l; *Helicobacter pylori* antigen in stool, negative. Inductively coupled plasma mass spectrometry (ICP-MS) analysis (results still pending at that time) revealed: inorganic arsenic (iAs) in the blood (<0.013 µmol/l); iAs in the morning urine (116 nmol/l); iAs in the afternoon urine (47 nmol/l); inorganic phosphorus (iP) in the morning urine (5.7 mmol/l); iP in the afternoon urine (2.7 mmol/l) (table 1).

With the suspected diagnosis of chronic arsenic intoxication (CAsI) [2, 3], the patient was advised to stop taking the arsenic-containing globules immediately, and 300,000 IU cholecalciferol (vitamin D_3) was administered intramuscularly. In addition, pantoprazole 40 mg b.i.d. was prescribed for the first week with dose tapering during the second week, and magnesium in the evening. The patient was informed about the suspected diagnosis in detail.

In the follow-up visit on 24 May 2018, the patient reported a significant reduction of the symptoms she had being complaining of; she felt more alert and could concentrate better. Although she still could not sleep well, she did not wake up in the night as she had used to do. Now and then, she had a little bit of a pinching sensation in her stomach. She was taking pantoprazole 40 mg twice daily and magnesium once daily and she was not taking arsenic globules anymore.

In the follow-up visit on 20 June 2018, she reported that, in the previous 2 weeks, she had taken the arsenic-containing globules again, on her own initiative and on a sporadic basis, because of abdominal pains. She again had a lot of flatulence and permanent pain in the lower abdomen on the right side with motion-associated radiation toward the navel and flanks. Again, she was having difficulty sleeping because of leg cramps and abdominal pains. When reviewing the CAsIDS (Chronic Arsenic Intoxication Score) criteria [3] the patient admitted to having the following symptoms since the end of 2017: loss of appetite, nausea, abdominal pains, diarrhoea, increased feeling of thirst with less micturition, weight gain, irregular menstruation, fatigue. Since about half a year ago, she reported having episodes of a strange discoloration and a cold feeling of both hands with a furry feeling. In the last 2 to 3 months, her lifelong eczema had progressed to her feet. Since January 2018, she had itching and tears in her eyes. For about 1 to 2 weeks, she had increasingly dizziness, especially while standing up. On physical examination, the blood pressure was 132/81 mm Hg, pulse 66 bpm, body weight 77.9 kg (with clothes), body height 158 cm,

Table 1: Patient's characteristics before treatment as of 17 May 2018 (age 16.5 years), and after treatment as of 12 October 2018 (age 16.9 years).

Age (years)	BH (m)	BW (kg)	BMI (kg/m^2)	eSW (g)	eSP (g)	iAs, blood (µmol/l)	iAs, morning urine (nmol/l)	iAs, afternoon urine (nmol/l)	iP, morning urine (mmol/l)	iP, afternoon urine (mmol/l)	As:P (w/w)
16.5	1.58	75 (62)	30 (25)	4340	562	<0.013	116	47	5.7	2.7	5.6 ×10^{-5}
16.9	1.58	77 (62)	31 (25)	4340	562	–	ND	50	10.4	27.9	1.6 ×10^{-5}

BH = body height; BW = body weight (between brackets: ideal weight considering the patient's large body frame); BMI = body mass index; eSW = estimated skeleton dry weight; eSP = estimated skeleton P-content; iAs = inorganic arsenic; iP = inorganic phosphorus. ND = non-detectable. Figures are rounded-up. See methods section for equations.

and she showed a non-pitting oedema of the legs. Her serum folate concentration was 7.8 nmol/l, which is below normal. ICP-MS analysis of the homeopathic globules yielded an average arsenic content of 0.85 ± 0.08 ng of arsenic per globule.

The patient was informed anew about CAsI, and absolute avoidance of arsenic-containing preparations was recommended again. An *ex juvantibus* therapy was started, with torasemide 10–20 mg once daily in the morning; thiamine (vitamin B_1) 300 mg, magnesium and folic acid 5 mg each once daily in the evening. On-demand medication included metamizole and simeticon.

Arsenic was undetectable along 4 cm of a sample of the patient's nuchal scalp hair shafts collected on the 12 September 2018. At the follow-up visit of 12 October 2018, iAs was undetectable in the morning urine, iAs concentration in the afternoon urine was 50 nmol/l (table 1), and the patient's complaints had almost all disappeared.

Discussion

The patient's clinical and laboratory findings are compatible with chronic iAs intoxication (CAsI) [3], and it is shown here that one bottle of the arsenic-containing homeopathic globules that she consumed indeed contains 1.7 µg of iAs (1 bottle x 2000 globules / bottle x 0.85 ng iAs per globule = 1.7 µg iAs). For comparison, the current US federal arsenic standard for drinking water is 10 ppB, which amounts to a dose of 30 µg per day when 3 litres of water are consumed per day [4]. Thus, the iAs concentration in the globules is a minimal, but not insignificant amount, that is still worth discussing as the significance of very low levels arsenic is still unclear and regulatory thresholds are not based on hard toxicological data.

The causality of this association cannot be proven, but there is measurable inorganic arsenic in these globules and this is a surprise, even if the amount is minimal and lower than current food allowances. Intoxication from other highly diluted (D6) components of the homoeopathic globules including *Cephaelis ipecacuanha*, inorganic mercury and *Podophyllum* sp. is considered unlikely or atypical. Other components such as xylitol and calcium carbonate are not known to cause the symptoms presented by the patient.

The causal link between chronic iAs exposure and the patient's nonspecific systemic symptoms is nevertheless suggested by circumstantial evidence pointing to the disappearance of CAsI signs and symptoms after therapy including interruption of the exposure. Chronic iAs exposure is accepted as a cause of a number of disorders, including respiratory, haematological, neurological, cardiovascular, renal, metabolic and endocrine diseases, and various types of cancer (arsenic and several of its compounds are listed in Group I of carcinogens from the International Association for Research on Cancer) [5]. Some signs and symptoms, including obesity [6], fatigue [7, 8] and anxiety [9, 10], are associated with chronic iAs exposure and they are diagnostic criteria that make up the body of clinical and laboratory evidence of CAsI. As pointed out in an extensive review, safe levels of chronic biological exposure overlap with concentrations that cause health effects or measurable impairment of body function over a wide range, and when detected levels of a given metal are in a range held to be normal, exclusion of toxic effects and poisoning requires additional consideration of clinical findings [11].

The presence of urinary arsenic at very low concentrations in the patient is less problematic, since associations between urinary arsenic at very low concentrations and increased morbidity and mortality have been described for a number of diseases. It has been found, for example, that the threshold for diabetes is 12 µg/g creatinine [12] and the threshold for cardiovascular disease is 7 µg/g creatinine [13]. For several types of cancer, including lung, prostate and pancreatic cancer, the associations between urinary arsenic and morbidity and mortality have been described as dose dependent, without a threshold [14]. In conclusion, there is no such thing as a safe chronic exposure threshold for iAs. Also, arsenic is the most persistent environmental toxicant affecting exposed populations around the world [15–17], and humans are more susceptible to the toxic effects of arsenic than any other mammal studied so far [18].

In addition, osteoresorptive arsenic intoxication (ORAI) is related to bone metabolism in patients chronically exposed to iAs [2]. The elevated ALP activity observed in the patient has been described in several epidemiological studies of CAsI [19–21] and it is probably caused by the competitive inhibition of phosphatases by arsenic [22–24]. In an experiment with growing and finishing pigs, high dietary arsenic elevated the activities of ALP, GGT, GPT, and decreased total protein, urea nitrogen, creatinine, triglycerides and average daily gain, as well as increasing feed gain ratio and the retention of copper, iron and zinc in the viscera [25].

On the assumption of an average osteoresorption rate of 30% per year [26–28], it must be conceded that the risk of chronic ORAI is elevated in the patient. The re-assessment of risk in conditions of increased osteoresorptive activity is indicated. The patient should undergo periodic medical follow-up, especially in the following conditions that increase the osteoresorption rate and consequently increase the release of arsenic from the bones: prolonged rest; stress as in strenuous physical exercise with energy restriction and sleep deprivation; undernourishment as well as malnutrition; high salt intake as well as chronic hyponatraemia; insufficiency or deficiency of 25(OH)D (the storage form of vitamin D), as well as excess of $1,25(OH)_2D$ (the active form of vitamin D), as in granulomatous diseases such as sarcoidosis and tuberculosis; diabetes; infection and inflammation; gonadal dysfunction including decreased oestrogen production; hyperthyroidism; hyperparathyroidism; long-term corticosteroid therapy; endogenous hypercortisolism; cancer and bone metastases.

On a final note, the failure in detecting arsenic in the patient's hair can be attributed to the very low iAs concentration found in her blood, which might have allowed virtually all iAs to be methylated and consequently not to be incorporated into keratin [29]. As neither hair nor fingernails are long-term iAs storage compartments, osteoresorptive arsenic is the preferred biomarker of CAsI [3].

Therapy of arsenic intoxication

The most effective therapies of acute arsenic intoxication are removal of the exposure source and adequate ventilation and hydration, with close monitoring of the cardiorespiratory, haematological and renal status. The presently available chelation therapies have questionable value as they may aggravate the clinical status of poisoned patients [30].

Whereas there is as yet no proven therapy for CAsI, stopping the environmental exposure as well as curtailing the intoxication routes and mechanisms remain as valid measures. Correcting an eventual hypophosphataemia may decrease the As:P ratio by competitively displacing inorganic arsenic in the cell, thereby decreasing the iAs toxicity [31]. In ORAI, adequate supplementation with calcium and vitamin D (cholecalciferol) as well as antiosteoresorptive therapy with a bisphosphonate have been shown to reduce the release of iAs from the skeleton, thereby reducing iAs intoxication [2].

Approaches to boost mitochondrial bioenergetics [32], including boosting pyruvate dehydrogenase activity with thiamine [33] and magnesium [34], as well as using methylene blue as an alternative mitochondrial electron transfer [35] await experimental and clinical testing.

The use of exogenous and/or endogenous antioxidants [36, 37] is also a concept that deserves experimental and clinical verification. Activation of antioxidant systems and antioxidative agents such as glutathione, manganese superoxide dismutase and n-acetyl-cysteine hold promise to mitigate at least part of the deleterious effects of reactive oxygen species and CAsI [38].

Supplementation with zinc [39] and selenium [40] have been postulated as beneficial, and folic acid has been associated with increasing iAs methylation capacity and lowered disease risk in human studies [41].

Release of arsenic species from proteins is an approach that has been pursued experimentally in analytical chemistry [42], but the *in vitro* conditions shown to release arsenic from proteins are too harsh to allow for any clinical application.

Conclusion

The arsenic-containing globules are considered a “homeopathic” formulation according to the 18th century-old idea propounded by German doctor Samuel Hahnemann who believed that “like cures like” and that minute concentrations of a particular toxin could cure the very same symptoms it would cause in larger doses. Here we show that Hahnemann’s homeopathic concept does not work for a substance like arsenic. Since there is no safe dose for iAs, sustained oral exposure to this toxicant even at ultra-low (part per billion, ppB) level can be toxic. It is concluded that an avoidable toxicant such as iAs, for which no scientific safe dose threshold exists, should be avoided and not be found in over-the-counter medications.

Methods

Initial ICP-MS analyses of total arsenic (iAs) in blood and iAs and phosphorus (P) in urine were routinely performed by Labor Risch (Liechtenstein). ICP-MS analyses of iAs in the homeopathic globules and scalp hair, as well as follow-up analyses of iAs and P in urine, were performed by the Trace Element Speciation and Environmental Chemistry Group at the Institute of Geography at the University of Bern, Switzerland. The samples were digested using nitric acid and hydrogen peroxide in a microwave (MARS 6 from CEM, Charlotte, North Carolina, USA) and analysed in continuous flow ICP-MS (7700x Agilent, Santa Clara, California, USA). The limit of detection for iAs in hair with the ICP-MS method and dilutions was 0.135 mg/kg, and in urine of 1.69 µg/l. Spiking of iAs in the samples was conducted as quality control. To estimate the skeleton dry weight (eSW), the equation eSW (g) = 0.07 × (BW) × 1000 was used. The skeleton P content (eSP) was calculated by the equation eSP (g) = eSW × 0.7 × 0.185, assuming 70% bone mineral matrix and 18.5% P-content thereof.

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