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‘Colouring’ wipes phenomenon: a peculiar skin pigmentation induced by ascorbic acid observed during lockdown

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Summary

During the SARS-CoV-2 (COVID-19) pandemic, an unusual outbreak of yellow–brown pigmentation on the skin of children was reported. Because of the restrictions on movement promulgated during the lockdown, most consultancies were performed using teledermatology. Data concerning personal care products and application of topical substances were collected, which revealed use of the same brand of wipes for all patients. A liquid chromatography–mass spectrometry analysis was performed to compare the components of the wipes before and after the observation of the pigmentation, in order to detect the responsible substance. This analysis revealed a level about 10-fold higher than normal of ascorbic acid and its oxidation products (dehydroascorbic acid and L-threonic acid) in the wipes associated with the pigmentation. These ‘colouring wipes’ represent a peculiar but harmless phenomenon that highlights the importance of careful questioning about personal care products used by patients.

An unusual outbreak of yellow–brown pigmentation on the skin of children was reported by paediatricians and dermatologists in 2020.[1] During the COVID-19 lockdown, we observed an analogous phenomenon in children in Emilia-Romagna, a region in northen Italy. The aim of our study was to investigate the cause of this phenomenon.

Report

In total, 15 children came to our attention because of a sudden onset of yellow–brown pigmentation on their skin (Fig. 1). The 15 children comprised 6 boys and 9 girls aged between 2 months and 4 years, and among these were two pairs of siblings. Of the 15 cases, 6 presented to our paediatric dermatology service, while the remaining cases were evaluated through teledermatology consultancies. The mean time between the pigmentation onset and the visit or teledermatology consultancy was 7 days (ranging 2–14 days).

All the children showed good general health and their general and dermatological medical histories were unremarkable, except for three patients with a history of atopic dermatitis. The sites involved were the buttocks (15/15 patients), abdomen (10/15), back (8/15), thighs (7/15), hands (7/15), arms (3/15) and face (5/15). None of the patients had any associated symptoms, including itching or burning sensation. In three cases the pigmentation was also observed on the parents’ hands. The pigmentation was easily removed with soap and water, although in some cases a brownish halo lasted for a few days.

Data about personal care products and application of topical substances, including detergents, creams, perfumes and baby wipes, were obtained. The parents denied using perfumes or topical tanning products. The detergents and creams varied between the

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children, and the only product common to all the patients was a particular brand of baby wipes. Interestingly, these wipes had been regularly used for 4 of the patients, while for the remaining 11 cases the wipes had only been recently introduced to the toilet routine, after the lockdown started. The appearance, colour and odour of the wipes were normal, and a 'strange' smell was reported in only one case. The wipes were therefore hypothesized to be responsible for this phenomenon, despite their apparently normal characteristics.

We reported this adverse event to the manufacturing company and a chemist was contacted to investigate if there was any ingredient that might responsible for this pigmentation.

All the substances that make up the wipes were analysed by liquid chromatography–mass spectrometry (LC-MS) analysis, in order to detect any difference in the chemical species composition among the wipes of the same brand, produced before (samples 1176 and 1177; the typical products) and after (samples 1173–1175; the atypical products) the detection of the skin pigmentation.

LC-MS analysis of nonvolatile substances was carried out on the wipes as follows. The sample was prepared by taking a known quantity of the sample (5.00 g) and subjecting it to extraction with 10 mL of pure (≥ 99.9%) methanol by ultrasonic sonication for 3 h at 60 °C. Once the extraction was finished, 1 mL of methanol was removed for instrumental investigation using the LC–quadrupole time-of-flight (LC-QTOF) technique (Agilent HPLC 1290 chromatograph coupled with an Agilent 6530 AccurateMass QTOF-LC/MS mass spectrometer, using an Agilent Eclipse Plus C18 RRHD column 1.8 μm 2.1 × 50 mm; flow rate 0.3 mL/min; injected volume 1 μL; eluent A contained H_2O + 0.05% formic acid + 5 mmol/L ammonium formate; eluent B contained methanol 4 mol/L, acetonitrile 1 mol/L + 0.05% formic acid + 5 mmol/L ammonium formate).

Comparing the two groups of wipes, there were no significant difference in any of the substances analysed with the exception of ascorbic acid (AA) and its oxidation products. In fact, the LC-QTOF analysis showed a level about 10-fold higher than normal for AA (Fig. 2), dehydroascorbic acid (DHAA) (Fig. 3) and L-threonic acid (L-TA) in the atypical wipes, implying that these were the substances responsible for the yellow–brown pigmentation.

AA (vitamin C) is an essential micronutrient with antioxidant properties, which is involved in many enzymatic and nonenzymatic reactions. It acts as a cofactor in tissue repair, neurotransmitter production amd immune system function, and as a scavenger of free radicals produced after ultraviolet radiation exposure.[2–4]

Figure 1 A brown pigmentation on the abdomen in a 1-year-old boy.

Topical vitamin C compounds are used for their photoprotection, antiageing, depigmenting and anti-inflammatory actions, and for stimulating the synthesis of collagen.[2,5] They have been shown to be safe, and their minor adverse events (AEs) include a yellowish discolouration of the skin, yellow chromonychia, hair hypopigmentation and staining of clothes.[5,6]

AA is also used as an antioxidant in the processing of the raw materials of wipes. In our cases, a level of this substance 10-fold higher than normal was observed. AA is colourless, although DHAA and L-TA display a yellow–brown pigmentation. Light and oxygen exposure, associated with skin contact induce the formation of the oxidation products from AA, explaining the normal appearance of the wipes and the latency between their use and the development of the pigmentation.

None of these substances represent a health hazard. In fact, when the pH is > 3.5 (skin has a pH of 4–6), AA undergoes an ionic charge, which prevents its

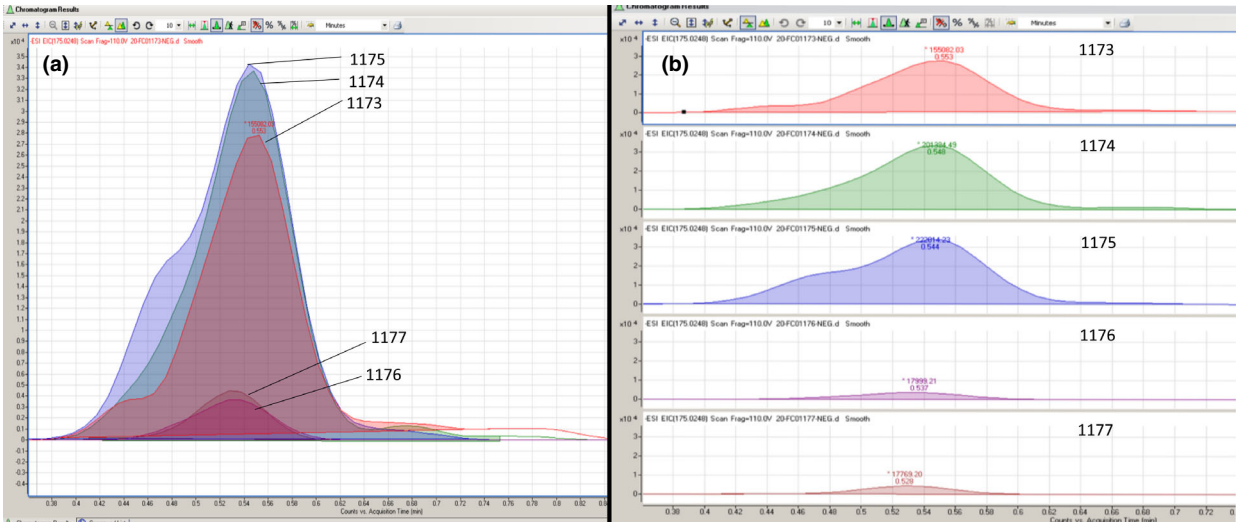

Figure 2 (a) Overlapping and (b) separate graphs of the liquid chromatography–mass spectrometry analysis of ascorbic acid. Typical products (those associated with skin pigmentation) are represented by samples 1173–1175, while the atypical products (not associated with skin pigmentation) are represented by samples 1176–1177.

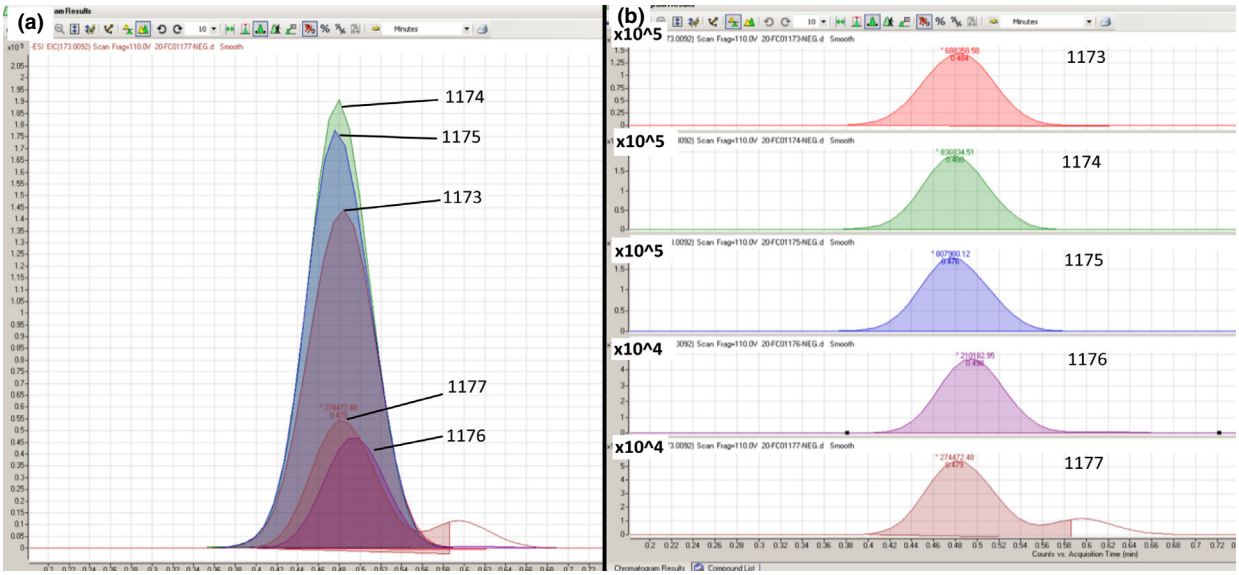

Figure 3 (a) Overlapping and (b) separate graphs of the liquid chromatography–mass spectrometry analysis of dehydroascorbic acid. Atypical products (those associated with skin pigmentation) are represented by samples 1173–1175, while the typical products (not associated with skin pigmentation) are represented by samples 1176–1177.

passage through the stratum corneum of the skin.[2,7] Therefore, AA, DHAA and L-TA settle on the skin, without systemic absorption.

Another possible mechanism might be the Maillard reaction, which occurs between carbohydrates and amines and represents the mechanism of action of self-tanning products. AA can react with proteins and peptides in the stratum corneum, leading to brown pigmentation. However, in our cases, the pigmentation was very easy to remove, leading us to consider that it is simply a consequence of the deposition of AA and its metabolites on the skin.[8]

The differential diagnoses of yellow–brown skin pigmentation include pigmented contact dermatitis (PCD) and chromhidrosis. PCD is a variant of contact dermatitis in which inflammatory aspects are slight, and

the subsequent skin hyperpigmentation represents the main finding. However, in the reported cases the pigmentation persisted for months or even years, whereas in our patients the staining was easily removed with soap and water and lasted a few days at most.[9] Chromhidrosis is characterized by the secretion of coloured sweat, while pseudochromhidosis is a variant resulting from the interaction of colourless eccrine sweat with other compounds, such as metal salts, dyes or pigments.[10]

Even though it was a harmless event, the 'colouring wipes' phenomenon raised concern among the children's families and paediatricians. Following our report, the manufacturing company withdrew the batches of the product responsible for the pigmentation from the commercial market. The high levels of AA were attributed to a problem during the manufacturing process.

Interestingly, in 11 of the 15 patients, this event came about following the changes in purchasing habits of their families after lockdown. In fact, in order to leave the house only for primary needs, the families bought their personal hygiene and care products at the supermarket, thus introducing new products into their children's hygiene routine. Moreover, the enhanced attention towards hygiene led to an increase in the use of wipes in these children.

In conclusion, we report an unusual finding of yellow–brown pigmentation in children, caused by AA in wipes. This report highlights the importance of a careful collection of data about personal care products, which are often under-investigated, by clinicians.

Learning points

- In Italy, during the COVID-19 lockdown, an unusual outbreak with yellow–brown pigmentation on the skin of children was observed.
- In our study, baby wipes were identified as the product common to all the children.
- LC-MS revealed AA as the causative agent.
- Topical AA (vitamin C) compounds are widely used in dermatology, and have a good safety profile, with minor AEs including a yellowish discolouration of the skin, yellow chromonychia, hair hypopigmentation and staining of clothes.
- In cases of skin pigmentation, careful collection of data about personal care products may be required in order to achieve the correct diagnosis.

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