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LETTER TO THE EDITOR

Bismuth-related acute neurotoxicity as stroke mimic: a case report

Amelia Brigandì[1,2] · Vincenzo Rizzo[1] · Vanessa Ziccone[1] · Paolo Girlanda[1,2]

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Stroke mimics (SM) are non-vascular conditions presenting with an acute neurological deficit simulating acute ischemic stroke [1]. We present a patient with sudden onset of neurological signs mimicking a stroke who resulted intoxicated by bismuth subcitrate.

Case report

A 51-year-old woman arrived to our E.R. in the suspicion of acute ischemic stroke. She had presented headache followed by numbness and sudden loss of strength in her right limbs 2 hours before. She was alert, oriented, collaborating, and reported double vision when she looked on the right. Neurological examination revealed a right facio-brachio-crural moderate hemiparesis with associated ipsilateral hypoesthesia. Deep tendon reflexes were brisk and symmetrical; Babinski sign was absent bilaterally. Past clinical history discovered only Gilbert's Syndrome and chronic sinusitis. More recently she had manifested gastrointestinal problems (esophageal burning, epigastric pain). A gastroscopy performed about 7 days before revealed "Gastro esophageal reflux disease without mucosal lesions (NERD) and erythematous gastro-duodenitis" with a positivity for *Helicobacter pylori*. For this reason, as prescribed by a gastroenterologist, she had started therapy with Pylera®140/125/125 mg (Bismuth potassium subcitrate + Metronidazole + Tetracycline hydrochloride) [2] 3 capsules three times a day, together with omeprazole 40 mg 1 tablet a day.

Before admission, the patient had taken 18 tablets. Her blood tests (complete blood count, kidney and hepatic function, blood protein level, lipidic profile, C reactive protein, erythrocyte sedimentation rate) were in normal range except for mild increase of total cholesterol, LDL cholesterol, direct bilirubin, and white blood count with neutrophils in leukocyte formula. The EKG was normal. Non-contrast CT brain scan excluded hemorrhage and was negative for acute events. She was hospitalized in our Neurology Department. According to the Italian ISO-SPREAD guidelines [3], we performed brain MRI that showed previous parcellar ischemic lesions with no evidence of water diffusivity restriction related to acute ischemic events. The arterial spin labeling study did not demonstrate hypo-perfusion areas. Angio-MRI did not show anomalies of arteries and vessels, neither vascular malformations nor aneurysms. In the clinical suspicion of acute neurotoxicity, Pylera therapy was immediately stopped. Other instrumental examinations were performed: Transcranial Doppler Ultrasonography (no shunt) and Supra-aortic Trunks Color Doppler Ultrasonography (absence of atherosclerotic plaques). Screening for rheumatoid factor, folic acid, B_{12} vitamin, and autoimmune disorders was in range, except for a low pathological level of ANA and anti-phospholipids antibodies. Thyroid function showed a slight reduction of T3 values with a high titer of anti-thyroglobulin antibodies. We performed blood and urinary dosage of the bismuth. Bismuth's levels resulted much higher than the national recommended standards (blood bismuth concentration: 7.07 μg/L [0.02–0.06], urinary bismuth concentration 30.3 μg/L [0.8–1.6]). The patient refused lumbar puncture in order to perform CSF evaluation. By day 3 of admission, the patient presented a marked improvement in strength with regression of diplopia and headache. She was released from our

Amelia Brigandì and Paolo Girlanda contributed equally to this work.

✉ Amelia Brigandì
amelia.briga@hotmail.it

Vincenzo Rizzo
enzo.rizzo@gmail.com

Vanessa Ziccone
zicconev@gmail.com

Paolo Girlanda
girlandp@unime.it

[1] Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy

[2] Movement Disorders Unit, AOU G. Martino, University of Messina, Via Consolare Valeria 1, 98125 Messina, Italy

department at day 7 with a minimal motor impairment in the right hand.

Discussion

The reported critical toxic threshold level of bismuth blood is 100 μg/L. Nevertheless in our patient, bismuth blood and urine tests have been performed 5 days after she was admitted and were still out of range for the Italian standard. According to the literature [4, 5], it is possible that the co-assumption of bismuth subcitrate with omeprazole together with the rapid increase of bismuth blood level derived from the numerous doses of Pylera in a very short time could be considered responsible for our "toxidrome." We considered the possibility of a deficiency of glutathione [6] in our patient, but no further tests and exams have been performed so far, or also a possible involvement of decreased T3 levels impacting the clearance rate of the drug. We excluded the possibility of an acute metronidazole intoxication as in the literature, there are reported cases of intoxication after a minimum of 10 days of therapy, always associated with radiological signs with an involvement of the dentate nuclei of the cerebellum, splenium of corpus callosum, dorsal pons, tegmentum of midbrain, vestibular nuclei, and basal ganglia at the brain MRI. We were also dissuaded from the blood test because the neurological examination did not show cerebellar signs or involvement of the peripheral nervous system. We used the Naranjo Algorithm (NA) for adverse drug reactions (ADRs) [7] in order to have a judgment of probability about our case. The score was 7 (doubtful 0, possible 1–4, probable 5–8, highly probable ≥ 9). The lesson that can be learnt from this reported experience is that even though the co-administration of bismuth (in maximum concentration with a Cmax above 50 ng/ml) with omeprazole and metronidazole is currently considered safe with regard to its neurotoxicity [8], this particular incidence of acute focal neurological signs was due to bismuth intoxication in the patient who had a history of decreased T3 levels. Further, caution should be practiced when using drugs containing bismuth for *H. pylori* eradication in such group pf patients.

Author contributions Amelia Brigandì: study concept and design, acquisition of data, analysis and interpretation, and critical revision of the manuscript for important intellectual content.

Paolo Girlanda: acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content, and study supervision.

Vincenzo Rizzo: study concept and design, acquisition of data, analysis and interpretation, and critical revision of the manuscript for important intellectual content.

Vanessa Ziccone: acquisition of data and analysis and interpretation.

Compliance with ethical standards

This article does not contain any studies with human participants performed by any of the authors.

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Vilela P (2017) Acute stroke differential diagnosis: stroke mimics. Eur J Radiol 96:133–144
2. De Boer WA (2001) A novel therapeutic approach for Helicobacter pylori infection: the bismuth-based triple therapy monocapsule. Expert Opin Investig Drugs 10:1559–1566
3. Gensini GF, Carolei A, Zaninelli A et al. SPREAD-Stroke Prevention and Educational Awareness Diffusion. Ictus cerebrale: Linee guida italiane di prevenzione e trattamento. In: ISO-spread [online] Available at: www.iso-spread.it. Accessed July 21, 2016
4. Treiber G, Walker S, Klotz U (1994) Omeprazole-induced increase in the absorption of bismuth from tripotassium di-citrato bismuthate. Clin Pharmacol Ther 55(5):486–491
5. Nwokolo CU, Prewett EJ, Sawyerr AM, Hudson M, Pounder RE (1991) The effect of histamine H2-receptor blockade on bismuth absorption from three ulcer-healing compounds. Gastroenterology 101:889–894
6. Yifan H, Yau-Tsz L, Godfrey C-FC, Hongzhe S (2015) Glutathione and multidrug resistance protein transporter mediate a self-propelled disposal of bismuth in human cells. PNAS [serial online] 112(11): 3211–3216 Available at: www.pnas.org. Accessed March 17, 2015
7. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt DJ (1981) A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 30(2):239–245
8. U.S. Food and Drug Administration (2007). Pylera ™ Capsules (bismuth subcitrate potassium, metronidazole, and tetracycline hydrochloride) 140 mg/125 mg/125 mg. https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/050786 s001lbl.pdf. Accessed 18 October 2018