JOURNAL OF PSYCHOPATHOLOGY
2019;25:231-235

M. Maiello, M.G. Carbone,
L. Dell'Osso, M. Simoncini, M. Miniati

Department of Clinical and Experimental Medicine, University of Pisa, Italy

Acute cognitive and psychomotor impairment in a patient taking forty different herbal products and dietary supplements: a case report

Summary

The use of dietary supplements and herbal medicines is spreading across many developed countries. Although patients without specific problems can administer most, relevant toxicities might occur with a reckless use of dietary supplements, especially when psychiatric or medical comorbidities are present. Limited research is available on these compounds. We describe the case of a suspected intoxication due to a reckless use of a number of dietary supplements and herbal medicines (forty different compounds) in a patient with a history of recurrent depression and gromerulonephritis, hospitalized for acute cognitive and psychomotor impairments.

Key words

Nutritional supplements • Herbal • Cholinergic syndrome

Introduction

The World Health Organization (WHO) and the United States (US) Dietary Supplements Health and Education Act, in the early '90, defined dietary supplements as a product (other than tobacco) that is meant to supplement the diet [1]. Both organizations include vitamins, minerals, herbs, botanical products, amino acids, or dietary substances in their definitions [2]. Since then, dietary supplements and herbal medicines are playing a growing role in health care. Vitamins and minerals are necessary for enzymatic reactions and bodily functions. It is well known that the lack of these compounds can lead to deficiency-related diseases [2]. However, by the arbitrary classification in *herbals'*and *other medicinal* products as *dietary supplements*, DSHEA obscured the fundamental differences between the two classes of products [3], even if there is no scientific basis for calling the *herbals supplements*. Authentic *supplements*, are multivitamins or calcium: they have nutritional value and are safe when used in recommended doses.

According to the 2006 American Association of Poison Control Center (AAPCC), there were a total of 972,073 significant adverse events due to the exposure to pharmaceutical products, with 6,809 major outcomes, 507 of whom resulting in deaths [4]. Of the above-mentioned adverse events, 76,364 (7.9%) were in some way related to the use of dietary supplements and vitamins, with 42 major outcomes (0.6%) and 3 deaths (0.6% of all deaths). Thus, despite the impressive widespread of these products, the adverse outcomes and deaths are reported as exceptional. Dietary supplements and herbal medicines seem to be relatively harmless when appropriately used, even if there is growing concern on both the interactions with concurrent drugs and the potential adulteration of such compounds. The Food and Drug Administration (FDA) had issued

Received: February 9, 2019
Accepted: May 13, 2019

Correspondence

Marco Maiello
Section of Psychiatry, Department of Clinical and Experimental Medicine, University of Pisa, via Roma 56, 56136 Italy
• Tel.: +39 050 996163 • Fax: +39 050 2219787
•E-mail: marcomaiello@aol.com

warnings about 300 tainted products that can cause serious adverse events, including stroke, organ failure and death [5]. Nonetheless, some adulterated products remain in the marketplace even after recalls [6].

Reports suggesting a relationship between an improper or a reckless use of these products and the onset of clinically relevant side effects are still under-estimated for a number of reasons, namely: a common perception in the patients' population that these products are inherently safe; the lack of information amongst medical professionals on their potential toxicity; the lack of systematic studies on such compounds when concurrent chronic medical diseases are present; the underestimation of their chronic abuse; the underestimation of the interactions between different herbals.

In this case report, we hypothesize that the use of a uncommon number of dietary supplements (forty different compounds at the same time) in a patient with a chronic kidney disease and a history of recurrent depression could be related to the onset of acute psychomotor and cognitive impairments. The presentation of this case report followed the CARE Guidelines [7] (2013). The patient signed an informed consent encompassing the data collection and presentation both for research and clinical purposes. However, even if the patient signed the above-mentioned consent form, all the information reported in this case report was anonymous.

Case presentation

A 38-year-old Caucasian male patient suffered from a recurrent major depressive disorder, with two major depressive episodes of moderate severity up to the present that remitted spontaneously. The family anamnesis regarding mental disorders was negative, and the patient did not use any psychotropic agents such as alcohol, nicotine or any illicit drugs. The patient lived in

TABLE I. *Timeline description of the case report.*

Psychopathological dimensions	2 weeks before hospitalization	On admission	During hospitalization before discontinuation of dietary supplements	1-week after discontinuation of dietary supplements	At discharge
Cognition	No signs or symptoms	Severe speech impairment; thoughts contents not described	Unable to provide useful information oh his cognitive state or performances (catatonia?)	Recovery with description of thoughts contents and mood states	Recovery with description of thoughts contents and mood states
Mood	Depressive mood Inner tension Emotional instability and liability	Unable to perform an evaluation or to describe his mood.	Unable to provide useful information oh his cognitive state or performances (catatonia?)	Patient able to perform a clinical interview. He described a subjective elevated mood, with decreased inner sense of tension	Euthymic
Circadian Rhythms	Severe insomnia	Severe insomnia	Severe insomnia	Improved sleep quality	Improved sleep quality. No insomnia
Psychomotor signs and symptoms	Widespread tremor Psychomotor retardation Rigidity	Severe psychomotor retardation Catatonia-like syndrome Rigidity Tremor Impaired gait	Severe psychomotor retardation Catatonia-like syndrome Rigidity Tremor Impaired gait	Improvement of psychomotor functions, with recovery	No evident or subjectively perceived psychomotor impairment
Other signs/ symptoms	Hyperhidrosis Bronchorrea	Sialorrhea, Hyperhidrosis	Sialorrhea, Hyperhidrosis	No hyperhidrosis No sialorrhea.	No thought abnormality

TABLE I. *Timeline description of the case report.*

Psychopathological dimensions	2 weeks before hospitalization	On admission	During hospitalization before discontinuation of dietary supplements	1-week after discontinuation of dietary supplements	At discharge
Cognition	No signs or symptoms	Severe speech impairment; thoughts contents not described	Unable to provide useful information oh his cognitive state or performances (catatonia?)	Recovery with description of thoughts contents and mood states	Recovery with description of thoughts contents and mood states
Mood	Depressive mood Inner tension Emotional instability and liability	Unable to perform an evaluation or to describe his mood.	Unable to provide useful information oh his cognitive state or performances (catatonia?)	Patient able to perform a clinical interview. He described a subjective elevated mood, with decreased inner sense of tension	Euthymic
Circadian Rhythms	Severe insomnia	Severe insomnia	Severe insomnia	Improved sleep quality	Improved sleep quality. No insomnia
Psychomotor signs and symptoms	Widespread tremor Psychomotor retardation Rigidity	Severe psychomotor retardation Catatonia-like syndrome Rigidity Tremor Impaired gait	Severe psychomotor retardation Catatonia-like syndrome Rigidity Tremor Impaired gait	Improvement of psychomotor functions, with recovery	No evident or subjectively perceived psychomotor impairment
Other signs/ symptoms	Hyperhidrosis Bronchorrea	Sialorrhea, Hyperhidrosis	Sialorrhea, Hyperhidrosis	No hyperhidrosis No sialorrhea.	No thought abnormality

a stable partnership (married 15 years before) without children and he was an employee, at the time of hospitalization. There was a relevant somatic comorbidity for hypertension and idiopathic glomerulonephritis. Before present hospitalization he was treated with ramipril (10 mg/day), bisoprolol (5 mg/day), doxazosin (8 mg/day), and amlodipin (5 mg/day). He reported also a period of treatment with corticosteroids due to the glomerulonephritis, few months before, but he was unable to describe more in detail dosage and treatment duration.

During the last two weeks before hospitalization, the patient had problems to fall asleep, with pronounced inner tension, depressive mood, emotional instability, dyspnoea, bronchorrea, and hyperhidrosis. These symptoms remarkably increased in the following days resulting in retardation, rigidity, widespread tremor, and mutism. Thus, the patient's wife contacted a psychiatrist. Psychosocial stress factors or any other circumstances that might have been plausibly involved in the causation of the described syndrome were ruled out. The psychiatrist diagnosed a catatonia with psychomotor retardation, and prescribed lorazepam (up to 15 mg/day), with no significant improvement. Then the patient was hospitalized (Tab. I).

On admission, the patient was drowsy, with a severe psychomotor retardation, oriented as to time and places but unable to give more detailed information on his mental state. He presented hypomimia, drooling, bradykinesia, impaired oculomotor movements (upward gaze and convergence), festinating gait, moderate intermittent tremor (both at rest and in motion), trunk and limbs rigidity, and oculo-cephalic reflex with optokinetic nystagmus. A specialist in internal medicine and a neurologist evaluated the patient. No acute medical condition was considered as related to clinical picture. The neurological signs and symptoms lead to a number of clin-

ical hypotheses: Posterior Reversible Encephalopathy Syndrome, limbic Encephalitis, Parkinsonism, Cortical Atrophy, Lewy-Body Dementia. A Magnetic Resonance Imaging (MRI) was performed. No abnormalities were found. Electroencephalography (EEG) showed mild generalized background slowing of cerebral electrical activity, probably due to the administration of lorazepam before hospitalization. SPECT DAT-SCAN was negative for nigro-striatal degeneration. PET scan identified a generalized reduction of cortical glucose metabolism in the occipital area on both hemispheres. Uptake of sub-cortical regions, thalamic regions, striatum and cerebellum was normal. Even a lumbar puncture was performed with negative results. According to the neurologist, there was no explanation for the described symptomatology.

Metabolic abnormalities were ruled out considering the normal ranges of complete blood count, serum glucose and electrolytes. Levels of vitamin B12 and folates were also within normal range. Blood culture urine cultures were negative, as well as neuro-degenerative proteins, (namely, neuro-oncogens, Ab Anti Hu, Ab Anti Yo, Ab Anti Ri, Ab Anti Anfifisin, Ab anti GAD, Ab Anti NMDA and Ab Anti VGKC). Negative blood tests and imaging led the clinicians to consider a Parkinsonism, even if the patient was not taking psychotropic medications. The patient was, then, empirically treated with levodopa and carbidopa, but no improvement was observed. During hospitalization, the patient had a gradual improvement only when a number of dietary supplements and herbal medicines he was taking at home and he was autonomously managing, were progressively discontinued, and when trihexyphenidyl was added for rigidity. The patient reported that, during the last 6 months, he added to ramipril, bisoprolol, doxazosin, and amlodipin a number of *natural* compounds that he was still taking during hospitalization, namely: syiybum marianum, curcuma longa, taurine, pneumus boldus, glutathione, phyllantus amarus, taraxacum officinal, crataegus oxycantha, allium sativum, leonurus cardiaca, betual verrucosa, fumaria officinalis, passiflora, actium lappa, betula alba, cynara scolimus, berberis vulgaris, cynodon dactylon, spirulina maxima, mellitus officinalis, ribes nigrus, marrubium vulgare, ruscus aculeatus, cupressus serpenvirens, proantocianidine, boswella serrata, elastine, dioscorea opposita, diosgenina, glucosamine, thea sinensis, epigallocatechine, cochiearia armoracia, glucorafanine, sulforafane, soja, genisteine, magnesium, zinc, selenium.

According to the patient, all these compounds were prescribed 6 months before by a *phyto-therapist*, as add-on to the usual treatments for gromerulonephritis and hypertension.

The discontinuation of these compounds during hospitalization was concomitant with a gradual improvement. Thus, the patient recovered regarding his mimic and speech ability; rigidity faded with a normal posture and motion. Mood was euthymic and no thought abnormality or residual cognitive impairment was found. The patient was then discharged.

Discussion

It's virtually impossible to affirm with certainty that psychomotor and cognitive impairments that lead to patient's hospitalization could have been directly provoked and sustained by the protracted use of the impressive number of dietary supplements and herbal medicines that the patient was taking during the last 6 months. However, no other possible explanations were found, and the discontinuation of such compound was concomitant with clinical remission.

Our hypothesis is that the protracted use of such compounds produced a clinical syndrome of cholinergic overstimulation, with bronchorrhea, respiratory muscle weakness and delayed neurotoxic effects with prevalent extra-pyramidal symptoms mimicking catatonia. Resolution after the discontinuation of herbal/nutritional supplements and with the administration of trihexyphenidyl is suggestive of such explanation.

To our knowledge, no studies have been conducted on the cholinergic effects of herbal supplements. However, It is well documented that patients with chronic illnesses (such as, in our case, a glomerulonephritis) are most likely to consume dietary supplements or herbal medications, with a significant risk of interactions [8]. A problem is also the contamination of herbals with microorganisms, fungal toxins such as aflatoxin, with pesticides and heavy metals that might be related with a cholinergic over-stimulation [9]. For patients taking multiple medications and dietary supplements or herbal medicines, physicians should look out for herb-drug interactions. However, It is impossible to check the interactions between forty different compounds (as in the described case) or to have reliable information on their purity. This case report, in our opinion, is raising questions on the importance of a more aware use of herbals, and on the importance of a more effective communication between health professionals and patients on the potential risks of products whose benefits, side effects, and reciprocal interactions are still largely unknown. Further research is necessary to investigate individual risk factors and preparation-specific characteristics that might predispose to the development of side effects, especially when herbal compounds are taken for a long time. Experience from our clinical unit suggests that most patients may use herbal products that are absent from the substances whose interaction risks are described in a systematic manner. Physicians might warn their patients on the potential risk linked to *herbal extracts,*

but in most cases without soundly based evidence from literature. We believe that promoting an active vigilance strategy for herbal compounds may help to generate better evidence, together with the promotion of specific education tools about the potential interactions of such compounds. The development of *integrative medicine centers* promoting interdisciplinary collaboration between patients, physicians, psychiatrists, and researchers formed in this field could be a possible future target.

Contributors

Marco Maiello, M.D. and Manuel Glauco Carbone written the case report; Liliana Dell'Osso M.D., and Marly Simoncini, M.D. were the case managers of the patient and contributed to describe the case report; Mario Miniati, M.D., revised the case report for intellectual content.

Conflict of interest.

The Authors declare to have no conflict of interest.

References

1. Dietary Supplement Health and Education Act (DSHEA). Public Law 103-417, 25 October 1994; Codified at 42 USC 287C-11.
2. Phua DH, Zosel A, Heard K. *Dietary supplements and herbal medicine toxicities-when to anticipate them and how to manage them*. Int J Emerg Med 2009 10;2:69-76. https://doi.org/10.1007/s12245-009-0105-z
3. Marcus DM. *Dietary supplements: what's in a name? What's in the bottle?* Drug Test Anal 2016;8:410-2. https://doi.org/10.1002/dta.1855
4. Bronstein AC, Spyker DA, Cantilena LR, et al. *2006 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS).* Clin Toxicol (Phila) 2007;45:815-917
5. Hamburg MA. *Letter to manufacturers of dietary supplements* (https://www.fda.gov/media/80108/download [21 April 2015]).
6. Cohen PA, Maller G, DeSouza R,, et al. *Presence of banned drugs in dietary supplements following FDA recalls*. JAMA 2014;312:1691.
7. Gagnier JJ, Kienle G, Altman DG, et al.; CARE Group. *The CARE guidelines: consensus-based clinical case reporting guideline development.* J Med Case Rep 2013;7:223.
8. Haller CA. *Clinical approach to adverse events and interactions related to herbal and dietary supplements*. Clin Toxicol (Phila) 2006;44:605-10.
9. Efferth T, Kaina B. *Toxicities by herbal medicines with emphasis to traditional Chinese medicine.* Curr Drug Metab. 2011;12:989-96.

How to cite this article: Maiello M, Carbone MG, Dell'Osso L, et al. *Acute cognitive and psychomotor impairment in a patient taking forty different herbal products and dietary supplements: a case report*. Journal of Psychopathology 2019;25:231-5.