Table 1 Summary of changes on dosage and plasma clozapine levels following clozapine intoxication with available leucocyte and platelet counts

Days	Clozapine dose (mg/day)	Clozapine level (μg/l) (n = 350-600 μg/l)*	Leukocyte count (x 10^9/L)	Platelet count (x 10^3/L)
D1 - Day before blood collection	350	980	10.1	235
D2	-	-	11.2	236
D3 - Upper gastrointestinal endoscopy: grade 4 reflux esophagitis				
D11	-	-	9.4	503
D17	250	633	6.9	481
D36	200	238	-	-
D43	200	192	-	-
D67 - Upper gastrointestinal endoscopy: fully healed esophagus				
D77	250	270	-	-
D84	250	263	-	-

tolerance since the start of treatment. Nefopam was also introduced for the management of hemorrhoid pain as needed, at 20 mg/d (po). After an additional 35 days of treatment with clozapine at 350 mg/d, one night the patient had hematemesis and diffuse abdominal pain. The next morning, she experienced vomiting and complained of epigastric pain. The patient was treated with domperidone (30 mg/d) and metoclopramide (20 mg/d, po, as needed). Clinical examination revealed reflux esophagitis (grade 4) associated with a hiatal hernia (4 cm). A blood test showed plasma clozapine levels of 980 μg/l (laboratory alert level is plasma concentration > 1,000 μg/L).[2] In this context, pantoprazole was introduced at a dosage of 20 mg/d, whereas domperidone was stopped after 1 week. Clozapine was gradually reduced to 200 mg/d. After 15 days, gastroesophageal symptoms had diminished and clozapine levels had fallen to 633 μg/L (therapeutic reference range = 350-600 μg/L).[2] About 2 months after esophagitis, a gastroscopic control was performed, demonstrating complete esophageal healing. Table 1 synthesizes the clozapine dose changes following intoxication along with the plasma levels of clozapine.

Some disorders affecting the gastrointestinal tract, including cases of esophagitis with hiatal hernias, have been reported with the use of clozapine, but very few have been published.[3] These gastrointestinal disturbances appear in connection with hypomotility and changes in digestive secretion induced by clozapine, as a result of its antiserotoninergic and anticholinergic properties.[3] Anticholinergic medications are often implicated in exacerbating gastroesophageal reflux disease by decreasing lower esophageal sphincter pressure and consequently causing or aggravating heartburn, but such conditions were not identified in our patient before the occurrence of esophagitis.

In our patient, the combined use of clozapine, tropatepine, and aripiprazole (stopped a week before the adverse effect but with a long half-life) may have enhanced the effects of clozapine by contributing to anticholinergic and antiserotoninergic effects respectively (nefopam was only administered on 2 days: 4 and 24 days before esophagitis). However, the dramatic increase in clozapine blood concentration seems sufficient to account for the adverse effect. To the best of our knowledge, this is the first case of clozapine-induced severe esophagitis correlated to a measured-level of plasma clozapine to be published in the literature.

Hervé Javelot,[1] Bruno Michel,[2] Divya Kumar,[3] Brigitte Audibert[3]
[1]*Clinical Pharmacy Service, Mental Health Establishment (EPSAN), Brumath, France.* [2]*Faculté de Pharmacie, Laboratoire HuManiS (EA 7308), Service Pharmacie - CHU de Strasbourg, Strasbourg, France.* [3]*Service G06, EPSAN, Brumath, France*

Submitted Jul 31 2015, accepted Nov 09 2015.

Disclosure

The authors report no conflicts of interest.

References

1 Naheed M, Green B. Focus on clozapine. Curr Med Res Opin. 2001;17:223-9.
2 Hiemke C, Baumann P, Bergemann N, Conca A, Dietmaier O, Egberts K, et al. AGNP consensus guidelines for therapeutic drug monitoring in psychiatry: update 2011. Pharmacopsychiatry. 2011;44:195-235.
3 Laker MK, Cookson JC. Reflux oesophagitis and clozapine. Int Clin Psychopharmacol. 1997;12:37-9.

Circadian rhythm disturbances and conversion to psychosis in ultra high-risk youth

Rev Bras Psiquiatr. 2016;38:177–179
doi:10.1590/1516-4446-2015-1859

Our group has recently showed that individuals in at risk mental states for psychosis and bipolar disorder (BD) have a poorer quality of sleep, start their daily activity later, and have a fragmented circadian rhythm compared with age and gender-matched healthy controls.[1,2] Another study shows that adolescents at high risk of developing psychosis are more prone to nocturnal awakening, which reduces sleep efficiency.[3] Nevertheless, the relationship

Table 1 Description of baseline sleep-awake cycle in three cases of at-risk mental states who transitioned to psychosis

Variable	First case	Second case	Third case
Age	13[-]	19	23
HO score*	27[-]	46	37
Epworth score[†]	5	1	10
Wake-up time (actigraphy)	05:07:19[-]	07:48:37	10:48:02
Wake-up time (PSG)	06:31:00	06:45:00	06:25:00
Best time to wake up (HO)	12:00:00	12:00:00	08:00:00
Start time of rest (actigraphy)	01:51:00	01:29:00	3:42:00[-]
Start time of rest (PSG)	23:07:00	22:54:00	23:58:00
Activity index in awake time	91.35	98.63[+]	85.24
Sleep minutes in awake time	65.5	25.1	140.06[+]
Rest duration	279.8[-]	374.57	400.21
Total sleep time (PSG)	372.5	442.5	335
Latency min (actigraphy)	4.6	7.95	29.05[++]
Latency min (PSG)	20	0.1	39
Rest duration on weekdays		413	
Rest duration on weekends		513.8	
Wake up time on weekdays (actigraphy)		06:52:52	
Wake up time on weekends (actigraphy)		09:30:20	
Wake up time on Saturday (actigraphy)		10:37:40	

HO = Horne-Östberg; PSG = polysomnography.
* Scores may range from 16 (eveningness) to 86 (morningness).
[†] Scores may range from 0 (low propensity to sleep) to 24 (high propensity to sleep.
[+] Highest value compared with the groups described in Castro et al.[1]; [++] second highest value; [-] lowest value.

between circadian abnormalities and risk of transition to psychosis remains poorly explored in the literature.[4] Here we present baseline data obtained at clinical assessment of sleep and circadian rhythm in three patients in at-risk states for psychosis who converted to a first episode of psychosis during follow-up.

The first case is a male patient with a strong preference for sleeping and waking up late. Polysomnography (PSG) and actigraphy showed extreme incompatibility between chronotype and social routine resulting in sleep restriction. The patient had a 93-minute sleep extension when sleep time was not restricted by routine activities.

The second case was classified as indifferent chronotype with sleep restriction (he slept 68 additional minutes during the PSG test compared to his normal routine). Furthermore, there was an increase of 100 minutes in total sleep time over the weekend compared to week days. The greatest difference in the amount of sleep was recorded on Saturdays. The data sets show chronic sleep restriction and advanced sleep phase imposed by routine.

The third case was an evening chronotype with no rigid routine, who was able to sleep and wake up late. Because he had an irregular wake-up pattern, a comparison between weekday and weekend sleep was not possible. During the active phase, 140 minutes were quantified as sleep by actigraphy, suggesting that the patient took a nap or rested at home. This finding was confirmed by the activity index, which shows 85.24% of uptime. These results indicate an active phase with rest, which was confirmed by high scores on the questionnaire on daytime sleepiness (Epworth; Table 1). The periods of rest during the awake time might be responsible for the long sleep onset latency (in both PSG and actigraphy). No sleep restriction was observed (actigraphy vs. PSG; Table 1).

The results showed a pattern of circadian rhythm disturbance in the three cases, indicating the need for a personalized sleep hygiene program. Tests such as actigraphy and PSG are important to identify whether rhythm disturbances are a result of the challenge between chronotype and routine, of sleep deprivation per se, and/or of daytime sleepiness. Further studies with longer duration records and other rhythms such as temperature of the wrist and exposure to light can provide more insights into circadian rhythm disturbances and their conversion to psychosis.

The synchronization of circadian rhythms can be increased by regular routine and more exposure to light.[5] Higher levels of physical activity should increase sleep rhythm amplitude and reduce sleep fragmentation. A sleep hygiene program can change the start and end times of sleep and its duration. Our results suggest that these changes to improve the circadian rhythm and sleep might help reduce conversions.

Bruno Gonçalves,[1,2] Juliana Castro,[3] Márcio A. Zanini,[1,2] Lia Bittencourt,[3] Ary Gadelha,[1,2] Graccielle R. Cunha,[1,2] Fernando M. Coelho,[3] Sergio Tufik,[3] Rodrigo A. Bressan,[1,2] Elisa Brietzke[1,2]
[1]*Programa de Reconhecimento e Intervenção em Estados Mentais de Risco (PRISMA), Departamento de Psiquiatria, Universidade Federal de São Paulo (UNIFESP), São Paulo, SP, Brazil.* [2]*Laboratório Interdisciplinar de Neurociências Clínicas (LiNC), UNIFESP, São Paulo, SP, Brazil.* [3]*Departamento de Psicobiologia, UNIFESP, São Paulo, SP, Brazil.*

Submitted Nov 17 2015, accepted Dec 04 2015.

Disclosure

The authors report no conflicts of interest. BG was supported by a post-doctoral fellowship from Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP; grant 2015/09421-4).

References

1 Castro J, Zanini M, Gonçalves Bda S, Coelho FM, Bressan R, Bittencourt L, Gadelha A, et al. Circadian rest-activity rhythm in

individuals at risk for psychosis and bipolar disorder. Schizophr Res. 2015;168:50-5.
2 Zanini MA, Castro J, Cunha GR, Asevedo E, Pan PM, Bittencourt L, et al. Abnormalities in sleep patterns in individuals at risk for psychosis and bipolar disorder. Schizophr Res. 2015;169:262-7.
3 Lunsford-Avery JR, LeBourgeois MK, Gupta T, Mittal VA. Actigraphic-measured sleep disturbance predicts increased positive symptoms in adolescents at ultra high-risk for psychosis: a longitudinal study. Schizophr Res. 2015;164:15-20.
4 Zanini M, Castro J, Coelho FM, Bittencourt L, Bressan RA, Tufik S, et al. Do sleep abnormalities and misaligned sleep/circadian rhythm patterns represent early clinical characteristics for developing psychosis in high risk populations? Neurosci Biobehav Rev. 2013;37:2631-7.
5 Gonçalves BS, Adamowicz T, Louzada FM, Moreno CR, Araujo JF. A fresh look at the use of nonparametric analysis in actimetry. Sleep Med Rev. 2015;20:84-91.

Anorexia nervosa presenting as a subacute sensory-motor axonal polyneuropathy

Rev Bras Psiquiatr. 2016;38:179–180
doi:10.1590/1516-4446-2015-1846

Anorexia nervosa is a psychiatric disorder characterized by abnormally low body weight associated with fear of gaining weight, body image disturbance, and restriction of caloric intake. It is categorized as restrictive when accompanied by a reduction in calorie consumption; or as purging when there is intentional overuse of diuretics, laxatives, or self-induced vomiting. Anorexia affects 0.3 to 0.9% of young women and 0.3% of young men.[1]

Despite the knowledge regarding the deleterious effects of anorexia nervosa on several organ systems,[2] neurological complications are still under-recognized. Only a few case reports so far have linked anorexia nervosa to brain atrophy[3] and peripheral neuropathy.[4,5]

Here we report the case of a young woman with subacute symptoms of peripheral polyneuropathy. Clinical and laboratory work-up identified vitamin deficiency secondary to hitherto undiagnosed anorexia nervosa.

A 24-year-old woman reported burning pain in her feet for three months. Two months after the onset of dysesthesia, she gradually developed a paralysis of the lower limbs. At this point, she had an orthopedic consultation which ruled out osteoarticular disease. Due to the worsening of motor and sensitive symptoms, she looked for medical assistance at the emergency department of the university hospital at Universidade Federal de Minas Gerais, Belo Horizonte, Brazil. She denied any previous disease and use of drugs.

Physical examination showed a very thin woman with body mass index of 14.9 kg/m^2. Neurological examination revealed absence of the deep reflexes in the lower limbs along with paraparetic gait and ataxia.

Laboratory workup did not reveal any abnormalities in complete blood count, electrolyte levels, renal, hepatic, and thyroid functions, and thiamine. Reduced levels of folate (2.05 nmol/L; normal values: $>$ 5.9 nmol/L) and vitamin B12 (190 pg/mL; 200-900 pg/mL) were detected. Electromyography confirmed the presence of symmetric sensory-motor axonal polyneuropathy. No change in gastric mucosa was evidenced by upper digestive endoscopy with biopsy.

Since the patient denied diarrhea or other symptoms that could indicate a malabsorption syndrome, a comprehensive approach tried to characterize her dietary habits. She claimed to be vegetarian, with occasional consumption of eggs and milk derivatives. She was afraid of gaining weight, and over the past three years persistently felt overweight. Moreover, she had morning episodes of vomiting after breakfast, and consumed progressively less food. The diagnosis of anorexia nervosa, restrictive subtype, was established.

Her vitamin deficiency was treated with intramuscular cyanocobalamin and oral vitamin B complex plus folic acid supplementation. Gabapentin (900 mg/day) was used for neuropathic pain. On follow-up she evolved with complete remission of sensory and motor symptoms, and recovery of normal weight and change of dietary habits under psychiatric and dietitian supervision.

The association between anorexia nervosa and peripheral neuropathy has rarely been reported.[4,5] A unique feature of the present case was the diagnosis of anorexia nervosa only after clinical and laboratory investigation of polyneuropathy. Until then, her neurological symptoms and weight loss were attributed to an undefined clinical condition. The precise diagnosis prevented unnecessary investigation, making clinical improvement possible.

Long periods of restricted food intake along with frequent vomiting may promote significant reduction of vitamin B12 acquisition. These facts, associated with the patient's vegetarian diet contributed to the development of this peculiar clinical presentation. Moreover, the absence of abnormalities on upper digestive endoscopy followed by histological analysis excluded the presence of local diseases that could justify B12 hypovitaminosis (e.g., atrophic gastritis). Clinical recovery with cyanocobalamin administration corroborates the causal assumption proposed. It should be mentioned that treatment of a case such as the one we described cannot be limited to vitamin supplementation and/or relieving of dysesthesia. Prompt weight restoration under dietary and psychiatric supervision is also essential. The severity of physical symptoms associated with anorexia nervosa possibly contributed to the patient's adherence to treatment and/or subsequent clinical improvement. Interestingly enough, a positive outcome regarding the eating disorder has also been reported for a severe case of anorexia nervosa presenting with peripheral neuropathy and Wernicke encephalopathy.[5]

The present case report highlights an atypical and severe form of anorexia nervosa. Early recognition and treatment of this illness might have prevented unnecessary neurological complications. Eating disorders must be considered in the differential diagnosis of vitamin deficiency syndromes.