Case report

Mania induced by isoniazid preventative therapy during steroid treatment for rheumatoid arthritis and organising pneumonia

Hiroyuki Nagano,¹ Tomoaki Miura,² Takeshi Ueda¹¹Emergency Medicine and General Internal Medicine, Rakuwakai Marutamachi Hospital, Kyoto, Japan²Department of Nephrology, Kyoto Okamoto Memorial Hospital, Kuze-gun, Japan

Correspondence to

Dr Takeshi Ueda;
maruta-GIM_ER-ueda@live.jp

Accepted 23 October 2019

SUMMARY

Isoniazid preventative therapy is widely used for latent tuberculosis infection. Isoniazid is highly effective but has many adverse effects, including neuropsychiatric. We describe the case of an 80-year-old woman with mania. She had received isoniazid preventative therapy during steroid treatment for rheumatoid arthritis and organising pneumonia for the previous 5 months. Her mania resolved after discontinuation of isoniazid. Adverse effects of isoniazid should be considered even if a long time has elapsed since the start of administration. Physicians other than infectious disease and respiratory specialists also must be aware of the adverse effects of isoniazid preventative therapy.

BACKGROUND

Secondary mania should be considered if manic syndrome develops for the first time after age 35. Many conditions are associated with secondary psychiatric mania.¹ They include cerebrovascular disease, neurodegenerative disorder, infectious disease and drug effects.

Latent tuberculosis infection is defined as a state of persistent immune response to prior acquired *Mycobacterium tuberculosis* antigens without evidence of clinically manifested active tuberculosis.² Suppression of cellular immunity by HIV infection, glucocorticoids, biological agents including tumour necrosis factor alfa inhibitors, chronic renal failure requiring dialysis and organ or haematological transplantation increase the risk of reactivating latent tuberculosis infection.^{3,4} Systemic testing (interferon-gamma release assays or Mantoux tuberculin skin test) and treatment should be considered for such patients.⁵ Isoniazid preventative therapy for 6–12 months is a widely used treatment for latent tuberculosis infection.⁶ Although highly effective, this drug has many associated adverse effects, including neuropsychiatric.⁷ Median time to appear neuropsychiatric adverse effect from initiation is about 3 weeks.⁸

We herein report the case of an 80-year-old woman with mania induced by isoniazid preventative therapy for 4 months during steroid treatment for rheumatoid arthritis and organising pneumonia.

CASE PRESENTATION

An 80-year-old Japanese woman was admitted to our faculty for the evaluation of abnormal behaviour

characterised by agitation, delusion, violence and disturbed sleep persisting for the past 1 month. Her speech was incoherent and disorganised. Prior to this, she had been independent and polite. A diagnosis of psychosis induced by prednisolone had been made in the outpatient department, leading to a dose reduction of prednisolone (10 mg) and a start of quetiapine (25 mg). However, her symptoms did not improve. Her medical history included rheumatoid arthritis, organising pneumonia and vasospastic angina. Isoniazid preventative therapy (isoniazid: 200 mg/day) had been started 5 months previously for latent tuberculosis infection while receiving steroid pulse therapy for organising pneumonia and prednisolone (45 mg). When she developed psychosis, her medication comprised prednisolone (17.5 mg), esomeprazole magnesium hydrate (10 mg), aspirin (100 mg), tacrolimus (1.5 mg), trimethoprim-sulfamethoxazole (40–200 mg), alfacalcidol (0.25 µg), diltiazem hydrochloride (100 mg), sodium risedronate hydrate (75 mg/month), pyridoxine (30 mg) and isoniazid (200 mg).

On physical examination, her body temperature was 37.2°C, respiratory rate was 20 breaths/min, and pulse was 115/min. Her oxygen saturation and blood pressure were normal. The general examination was within normal limits except for small-joint swelling of the hands. She was right handed. There was no neurological deficit (no focal weakness, cranial nerve involvement nor sign of meningeal irritation), but she was very agitated, restless and failed to obey verbal commands. Her body weight was 34 kg (42 kg when she had started isoniazid 5 months previously).

Her haemoglobin level was 11.5 g/dL, white cell count was $13.8 \times 10^9/L$, and platelet count was $365 \times 10^9/L$. Her white cell differential count was 35% lymphocytes, 18% monocytes, 44% segmented neutrophils and 3% band neutrophils. Blood chemistry test results were as follows: lactate dehydrogenase, 415 IU/L (normal range: 100–225 IU/L); aspartate aminotransferase, 22 IU/L (11–32 IU/L); alanine aminotransferase, 18 IU/L (3–30 IU/L); total bilirubin, 1.4 mg/dL (0.2–1.0 mg/dL); alkaline phosphatase, 183 IU/L (100–335 IU/L); blood urea nitrogen, 20.8 mg/dL (8–20 mg/dL); Creatinine, 0.68 mg/dL (0.4–1.1 mg/dL); NH₃, 38 mg/dL (30–85 mg/dL); Vitamin B₁₂, 32 ng/mL (24–66 ng/mL). The results of cerebrospinal fluid (CSF) examination were within normal limits: CSF proteins,

© BMJ Publishing Group Limited 2019. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Nagano H, Miura T, Ueda T. *BMJ Case Rep* 2019;**12**:e231919. doi:10.1136/bcr-2019-231919

Cerebrovascular disease	Q fever Prion disease Viral encephalitis	Medical disorder	Cough syrup
Basotemporal cortex, right		Carcinoid syndrome	Cyclobenzaprine
Binswanger's disease		Hyperbaric chamber use	Diet pills
Caudate, right		Hyperthyroidism	Donepezil
Cerebrovascular vasculitides		Postoperative state	Hydralazine
Inferofrontal cortex, right		Postpartum mania	Intereron alpha
Thalamus, right		Uremia and hemodialysis and dialysis	Iproniazid
Neurodegenerative disease	Cerebral neoplasms	dementia	Isoniazid
Alzheimer's disease	Diencephalic glioma, hypothalamic tumors	Vitamin deficiencies, eg, pellagra, B12 deficiency	Levodopa/sinemet
Fahr's disease	Orbitofrontal meningioma, bilateral		Lisuride, benzodiazepines
Frontotemporal dementia	Parasagittal meningioma	Drug	Metrizamide
Huntington's disease	Spheno-occipital tumor	α -adrenergic agent guanfacine	Mirtazapine
Neuroacanthocytosis	Temporal lobe glioma, right	Amphetamines and psychostimulants	Phencyclidine
Postencephalitic Parkinson's	Miscellaneous neurologic conditions	Antidepressants	Procarbazine
Wilson disease	Agrenoleukodystrophy	Baclofen	Procyclidine
Neurologic infection	Fragile X syndrome	Bromide	Sympathomimetics
AIDS	Kleine-Levin syndrome	Bromocriptine and dopamine agonists	Thyroid replacement
Creutzfeldt-Jakob disease	Klinefelter's syndrome	Cimetidine	Yohimbine
Cryptococcal meningitis	Metachromatic leukodystrophy	Cocaine	
Lyme disease	Multiple sclerosis	Codeine and paracetamol	
Neurosyphilis	Temporal lobe epilepsy, especially right	Corticosteroid	
	Thalamotomy and pallidotomy		
	Traumatic brain injury		
	Tuberous sclerosis		

Figure 1 Neurological causes of secondary mania.

39 mg/dL; sugar, 73 mg/dL; total leucocyte count, 1 lymphocyte/mm³). MRI of the head revealed no significant abnormality. The cultures of two sets of blood and cerebral fluid were negative.

OUTCOME AND FOLLOW-UP

We suspected isoniazid-induced psychosis, so it was discontinued on day 3. Subsequently, the psychotic symptoms resolved within 1 week and she became polite and independent. Because of the exacerbation of organising pneumonia, we increased the dose of prednisolone (20 mg) on day 8. However, the psychotic symptoms did not become aggravated. Then, we commenced rifampicin for latent tuberculosis, and the patient was discharged. Genotype analysis of the N-acetyltransferase 2 gene (NAT2) revealed two active acetylators, which indicates her fast acetylator status of NAT2.

DISCUSSION

We presented a case of mania induced by isoniazid preventative therapy for 4 months. This case highlights two important clinical issues: we should consider isoniazid as a cause of mania even if a long time has elapsed since the start of administration, and non-specialists encountering latent tuberculosis who are not used to prescribing isoniazid should be aware of the potential side effects.

First, many neurological and non-neurological conditions are associated with secondary mania (figures 1 and 2).¹ Steroid is a common cause of mania. However, in this case, steroid psychosis was unlikely because the mania did not resolve after steroid dose reduction and also did not exacerbate with a dose increase after hospital admission. Moreover, most reactions occurred in the course of steroid treatment (ie, within days).⁹ Isoniazid is one of the drugs associated with neurological side effects such as psychosis, peripheral neuropathy, dysarthria and seizure.^{10 11} The mechanism of isoniazid neurotoxicity is impairment of presynaptic gamma-aminobutyric acid production over time.¹² The era of antidepressants started with isoniazid, which caused euphoria and psychostimulation in patients with tuberculosis who received this drug.¹³ Psychiatric adverse effects of isoniazid are not rare. One study reported that the rate was 1.9 per 100 patients.¹⁴ The

Figure 2 Non-neurological causes of secondary mania.

onset of isoniazid psychiatric side effects ranges from 2 days to 10 months.¹⁵ Such effects are noted a median of 21 days⁸ and a mean of 35.8±13.3 days after the start of administration.¹⁶ We should exercise caution regarding such psychiatric side effects even if much time has elapsed since the start of administration. Indeed, in the present case, 4 months had passed since its initiation. In the present case, the dose may have become excessive due to her weight loss. The risk increases when the dose of isoniazid exceeds 5 mg/kg.¹⁷ Isoniazid is metabolised primarily by the polymorphic N-acetyltransferase 2 enzyme. There are three different phenotypic types depending on the acetylation rate: slow, intermediate and fast acetylators. In Japan, the prevalence of slow acetylator status of NAT2 is under 10%,¹⁸ which is a risk factor for isoniazid-induced toxicity.¹⁹ She had developed psychiatric symptoms despite her fast acetylator status of NAT2. Based on this, even in Japanese who often show a fast acetylator status, this side effect should always be borne in mind. Other risk factors associated with the psychiatric adverse effects of isoniazid include: advanced age, personal and family history of psychiatric disorders, malnutrition, alcohol intake, diabetes, renal and hepatocellular insufficiency, and hyperthyroidism.¹⁷ For patients with such risk factors, a 4-month regimen of rifampicin is an alternative.²⁰

Second, in the case of isoniazid preventative therapy, physicians other than infectious disease and respiratory specialists may be less knowledgeable about the side effects of isoniazid. According to the WHO, about 2–3 billion people are latently infected with *M. tuberculosis* on a global scale, and 5%–15% of them will show reactivation of tuberculosis in their lifetime.²¹ If they have risk factors for tuberculosis activation, preventative therapy should be provided. Along with those above-mentioned, risk factors include HIV infection, glucocorticoid use, biological agent use including tumour necrosis factor alpha inhibitors, chronic renal failure requiring dialysis and organ or haematological transplantation. Physicians encountering latent tuberculosis will increase in many fields, such as infectious disease, nephrology, rheumatology and general internal medicine. For example, the number of people living with HIV/AIDS in the world has been steadily increasing.²² The global prevalence of maintenance dialysis

increased 1.7 times from 165 (per million people) patients in 1990 to 284 in 2010.²³ In addition, the types and sales of biological agents are increasing,²⁴ and their indications for diseases are expanding in the world. In Japan, the types and sales of biological agents are also increasing,²⁴ and the number of treated cases of newly diagnosed latent tuberculosis infection increased from 2959 in 2007 to 7225 in 2017.²⁵ Since physicians other than infectious disease and respiratory specialists are increasingly administering isoniazid for the treatment of latent tuberculosis, even such non-specialists should be aware of this adverse effect.

In conclusion, we herein report a rare case of mania induced by isoniazid preventive therapy. Adverse effects of isoniazid should be considered even if a long time has elapsed since its initiation. Non-specialists must be aware of the adverse effects of isoniazid preventative therapy.

Learning points

- Secondary mania should be considered in the differential diagnosis of mania with onset in old age. Drug-induced mania is an important cause of mania in old age because it quickly remits following suspension of the drug.
- Isoniazid causes psychiatric side effects including mania even if much time has elapsed since the start of administration.
- Given the current increase in the rates of latent tuberculosis, every physician should become familiar with the neuropsychiatric side effects of isoniazid.

Contributors HN contributed to this paper by acquiring results and writing this case report. TM contributed by discussing the template. TU assisted in providing the idea for the case report, doing final edits and overlooking the case report.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Next of kin consent obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Mendez MF. Mania in neurologic disorders. *Curr Psychiatry Rep* 2000;2:440–5.
- 2 Mack U, Migliori GB, Sester M, et al. LTBI: latent tuberculosis infection or lasting immune responses to M. tuberculosis? A TBNET consensus statement. *Eur Respir J* 2009;33:956–73.
- 3 Getahun H, Matteelli A, Chaisson RE, et al. Latent Mycobacterium tuberculosis infection. *N Engl J Med* 2015;372:2127–35.
- 4 Singh JA, Saag KG, Bridges SL, et al. 2015 American College of rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol* 2016;68:1–26.
- 5 Getahun H, Matteelli A, Abubakar I, et al. Management of latent Mycobacterium tuberculosis infection: who guidelines for low tuberculosis burden countries. *Eur Respir J* 2015;46:1563–76.
- 6 Cohn DL. Treatment of latent tuberculosis infection: renewed opportunity for tuberculosis control. *Clin Infect Dis* 2000;31:120–4.
- 7 Denholm JT, McBryde ES, Eisen DP, et al. Adverse effects of isoniazid preventative therapy for latent tuberculosis infection: a prospective cohort study. *Drug Healthc Patient Saf* 2014;6:145–9.
- 8 Bhattacharyya S, Darby RR, Raibagkar P, et al. Antibiotic-Associated encephalopathy. *Neurology* 2016;86:963–71.
- 9 Dubovsky AN, Arvikar S, Stern TA, et al. The neuropsychiatric complications of glucocorticoid use: steroid psychosis revisited. *Psychosomatics* 2012;53:103–15.
- 10 Forget EJ, Menzies D. Adverse reactions to first-line antituberculosis drugs. *Expert Opin Drug Saf* 2006;5:231–49.
- 11 Kass JS, Shandera WX. Nervous system effects of antituberculosis therapy. *CNS Drugs* 2010;24:655–67.
- 12 Snively SR, Hodges GR. The neurotoxicity of antibacterial agents. *Ann Intern Med* 1984;101:92–104.
- 13 Ramachandran CT, Subramanyam N, Bar KJ, et al. Antidepressants: from MAOIs to SSRIs and more. *Indian J Psychiatry* 2011;53:180–2.
- 14 Psychiatric side effects of nonpsychiatric drugs. *Semin Psychiatry* 1971;3:406–20.
- 15 Iannaccone R, Sue Y-J, Avner JR. Suicidal psychosis secondary to isoniazid. *Pediatr Emerg Care* 2002;18:25–7.
- 16 Gülbay BE, Gürkan OU, Yildiz OA, et al. Side effects due to primary antituberculosis drugs during the initial phase of therapy in 1149 hospitalized patients for tuberculosis. *Respir Med* 2006;100:1834–42.
- 17 Menon VB, Shaji R, Pereira P, et al. Isoniazid associated psychosis: a case series of 3 patients. *IJOPP* 2017;10:142–6.
- 18 Sabbagh A, Darlu P, Crouau-Roy B, et al. Arylamine N-acetyltransferase 2 (NAT2) genetic diversity and traditional subsistence: a worldwide population survey. *PLoS One* 2011;6:e18507.
- 19 Huang Y-S, Chern H-D, Su W-J, et al. Polymorphism of the N-acetyltransferase 2 gene as a susceptibility risk factor for antituberculosis drug-induced hepatitis. *Hepatology* 2002;35:883–9.
- 20 Menzies D, Adjobimey M, Ruslami R, et al. Four months of rifampin or nine months of isoniazid for latent tuberculosis in adults. *N Engl J Med* 2018;379:440–53.
- 21 World Health Organization. Global tuberculosis report, 2018. Available: https://www.who.int/tb/publications/global_report/en/ [Accessed 05 Jul 2019].
- 22 Wang H, Wolock TM, Carter A, et al. Estimates of global, regional, and national incidence, prevalence, and mortality of HIV, 1980–2015: the global burden of disease study 2015. *Lancet HIV* 2016;3:e361–87.
- 23 Thomas B, Wulf S, Bikbov B, et al. Maintenance dialysis throughout the world in years 1990 and 2010. *J Am Soc Nephrol* 2015;26:2621–33.
- 24 Hiroto A. "Recommendations for the challenges and the further development of the bio-pharmaceutical industry". Available: http://www.jpma.or.jp/opir/research/rs_071/article_071.html [Accessed 05 Jul 2019].
- 25 The Research Institute of tuberculosis/JATA, The Tuberculosis Surveillance Center. "Transition of latent tuberculosis infection notifications by months" .. Available: <http://www.jata.or.jp/rit/ekigaku/toukei/nenpou/> [Accessed 05 Jul 2019].

Copyright 2019 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <https://www.bmj.com/company/products-services/rights-and-licensing/permissions/>
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

Customer Service

If you have any further queries about your subscription, please contact our customer services team on +44 (0) 207111 1105 or via email at support@bmj.com.

Visit casereports.bmj.com for more articles like this and to become a Fellow