



An elderly diabetic case of ochronosis with depression and chronic pain

Przypadek ochronozy z towarzyszącą depresją i przewlekłym bólem u osoby starszej z cukrzycą

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Abstract

Alkaptonuria (ochronosis) is a rare autosomal recessive disorder featuring a genetic error in the amino acid metabolism. A defect in the tyrosine metabolism results in the accumulation and deposition of homogentisic acid in connective tissue, causing a blue-black discoloration. Degenerative arthropathy of the spine, knee, and hip are common signs of ochronosis in older age. An association between ochronosis and depression has not previously been discussed in the literature. This case report describes a 69 year-old woman with diabetes mellitus, ochronosis, depression and chronic pain. (*Pol J Endocrinol* 2010; 61 (6): 710–713)

Key words: alkaptonuria, chronic pain, depression, elderly, ochronosis, diabetes mellitus

Streszczenie

Alkaptoniuria (ochronoza) jest rzadką, dziedziczną w sposób autosomalny recesywną chorobą metaboliczną, która polega na genetycznym defekcie przemiany aminokwasu, tyrozyny. Defekt ten powoduje gromadzenie się i odkładanie kwasu homogentyzynowego w tkance łącznej powodujące jej niebiesko-czarne zabarwienie. Częstymi objawami ochronozy w starszym wieku są zmiany zwyrodnieniowe stawów kręgosłupa, kolan i bioder. W bibliografii nie znaleziono opracowań dotyczących związku między ochronozą i depresją. Niniejszy opis przedstawia przypadek 69-letniej kobiety cierpiącej z powodu ochronozy, depresji i przewlekłego bólu. (*Endokrynol Pol* 2010; 61 (6): 710–713)

Słowa kluczowe: alkaptoniuria, przewlekły ból, depresja, wiek starszy, ochronoza, cukrzyca

Introduction

Ochronosis, often called alkaptonuric ochronosis, is a rare autosomal recessive metabolic disorder. It causes the accumulation and deposition of homogentisic acid oxidase (HGA), resulting in bluish black discoloration, calcification, chronic inflammation and degeneration of cartilaginous and related tissues throughout the body [1].

Depressive illness in older people is a serious and common health problem leading to unnecessary suffering, impaired functional status, increased mortality and morbidity, and excessive use of health care systems. Diagnosing depression in the elderly can be difficult because its symptoms overlap with those of other chronic illnesses, leading it to be frequently overlooked [2, 3]. Since depression is both treatable and associated with

increased mortality, it seems reasonable to make every attempt to diagnose patients.

Until now, the association between depression and ochronosis has not been discussed in the literature. This report presents the case of an elderly patient with ochronosis also suffering from depression and chronic pain.

Case report

A 69 year-old woman with an eight year history of ochronosis was referred to the clinic in May 2009, because of forgetfulness and chronic pain. She had experienced pain in all parts of her body for the previous two years and was taking analgesic/anti-inflammatory and myorelaxant drugs almost every day. She had derived benefit from these drugs, but nevertheless, she



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complained of appetite loss, fatigue, a feeling of hopelessness, sleeping difficulties, and an inability to enjoy life over the past year. Also, she had lost eight kilograms during this time.

Her family history showed two siblings who had been diagnosed with ochronosis. A review of her medical history revealed diabetes mellitus, hypertension, coronary artery disease, and ochronotic arthritis. Her surgical history was significant for cholecystectomy. Her present medications were metformine, amlodipine, valsartan, isosorbide-5-mononitrate, acetylsalicylic acid, and diclofenac sodium for pain. She had no known drug allergies and denied smoking or alcohol use. The subject was given an information sheet, and written informed consent was obtained from her.

On admission, physical examination revealed an older woman with depressive mood and severe pain secondary to neck and back, and bilateral knee pain. The patient's height was 153 cm, and weight 68 kg. Vital signs were as follows: arterial blood pressure, 140/90 mm Hg; pulse rate, 78 beats/min (regular and rhythmic); respiratory rate, 18 breaths per minute; room air oxygen saturation, 96%; oral temperature, 36.5°C.

She had a blue-black pigmentation on her sclera, the tip of her nose, ears, face, hands, feet, and, significantly, in palmo-plantar regions the palms of her hands and the soles of her feet (Fig. 1). Auscultation revealed that her lung sounds were clear bilaterally. On cardiac examination, the first heart sound was loud and there was a mid-systolic murmur (2/6) on apex and second intercostal space. Abdominal examination was normal. There was restricted range of motion in neck, knees, and lumbar spine. In addition, the coarse crepitus was associated with chronic systemic arthralgias and pain. Urine color was normal, but turned dark after 15 minutes. Her cognitive function remained intact and there was no evidence of a psychotic disorder. Her score on visual analog scale (VAS) was 9 (range 0–10) [4].

Laboratory data showed a normochrom-normocytic anaemia (hematocrit, 32.2%; haemoglobin concentration 10.9 g/dL). Other values revealed were: sedimentation rate 35 mm/h; serum glucose concentration — 105 mg/dL, HbA_{1c} levels — 6.4%, serum urea nitrogen concentration — 23 mg/dL, creatinine level — 0.9 mg/dL; uric acid — 2.9 mg/dl; sodium — 137.2 mmol/L; potassium — 4.55 mmol/L; calcium — 9.28 mg/dL; phosphorus — 3.48 mg/dL, total cholesterol — 197 mg/dL; triglyceride — 106 mg/dL; LDL-cholesterol — 139 mg/dL, HDL-cholesterol — 41 mg/dL; and albumin — 4.3 g/dL. Also, thyroid function tests were normal. Antero-posterior radiographies of cervical and lumbosacral vertebrae and knees showed the characteristic features of late stage ochronosis.



Figure 1.
Rycina 1.

Medical evaluation of her weight loss did not reveal a malignancy or malabsorption. Physical therapy was started for her neck, lower back, and knee pain. After ten sessions, her complaints had not resolved and so tramadole (50 mg/day) was added to the regime. In the control visit one month later, she stated that her pain was a little decreased, but not relieved (VAS 8/10). She was consulted by an experienced psychiatrist about her history of depressive complaints which were thought to be secondary to her pain. The patient completed a Yesavage Geriatric Depression Scale at the same visit. Her score on the scale was 12 (range 0–15, with scores greater than 11 indicative of depression) [5]. She was diagnosed as suffering from a major depressive disorder based on Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR) [6]. Thus, mirtazapine (15 mg/day) was started for depression and sleep disturbance. Effects of the treatment on pain and depressive complaints were observed in the control visit after one month (Yesavage score 8/15 and VAS 5/10). One month later, she was feeling less fatigued. Appetite loss, sleep disturbance and mobility had improved. However, she continued to feel hopeless and did not engage in her previous activities. To obtain an optimal result, the dosages of mirtazapine and tramadole were increased to 30 mg and 100 mg, respectively. In the control visit at the third month, her general complaints and pain had reduced, and depressive

Table I. Clinical course of the patient

Tabela I. Przebieg choroby u pacjentki

Date	Symptom	VAS	YGDS	Started therapy
Admission (Day 0)	Pain, forgetfulness, appetite loss, fatigue, hopelessness, inability to enjoy life, sleeping difficulties	9		
Day 3	Same complaints	9		Physical therapy (ten sessions)
Day 17	Same complaints	9		TMD (50 mg/day)
Day 30	Pain was a little decreased and other symptoms continued	8	12	TMD (50 mg/day) + MTZ (15 mg/day)
Day 60	Decreased pain, forgetfulness, hopelessness, and inability to enjoy life	5	8	TMD (100 mg/day) + MTZ (30 mg/day)
Day 90	Hopelessness and inability to enjoy life	3	3	TMD (100 mg/day) + MTZ (30 mg/day)

VAS — Visual analog scale (range 0–10); YGDS — Yesavage Geriatric Depression Scale (range 0–15); TMD — tramadole; MTZ — mirtazapine

symptoms were significantly improved (Yesavage score 3/15 and VAS 3/10). The patient reported that she felt “less depressed”, and attributed this to her antidepressant medication and pain-relief drug (Table I). She was followed-up in our clinic uneventfully.

Discussion

To the best of our knowledge, this is the first case describing combined depression and ochronosis in the literature. Management of this complex patient required simultaneous consideration of depression, sleep disturbance, and chronic pain due to ochronotic arthropathy.

This case report has a number of interesting findings that warrant further exploration and discussion. First, the patient's depressive symptoms were closely related to her pain from the ochronotic arthritis. Secondly, the combination of antidepressants and tramadole lifted the patient's depression and physical symptoms. Lastly, no reports on depression in ochronotic older patients have been published; our findings indicate that mirtazapine and tramadole may exert additional effects on ochronotic older patients.

First described in 1866, ochronosis is the accumulation of a pigment in the skin, cartilage, and collagenous tissues of the whole body. The genetic defect is mapped to the HGO gene on arm 3q1 and 18 genetic missense mutations are found to cause HGA oxidase aberrations [7]. The major clinical manifestations of this disorder are related to deposition of a pigment within the affected organs. Thus, a patient with ochronosis has pigmented skin and often has severe arthritis and pain, restrictive lung dysfunction, degenerative cardiovascular disease, and renal and prostatic calculi. At the present state of knowledge, no curable medical therapy is available for ochronosis and treatment is only based on symptomatology [1].

Depression can cause severe functional disability and even serious suicide attempts in the elderly. However, making a diagnosis of depression in the elderly can often be difficult in general practice. The idea that experiencing depressive symptoms is a ‘normal’ part of ageing, or that they are related to a physical disorder, cause a delay in diagnosis. There are many studies investigating the relationship between depression and physical disease. It has been shown that angina, diabetes, chronic bronchitis, arthritis, visual impairments, heart attacks and other cardiac diseases, rheumatism, lung diseases, cancer, and vascular events increase the risk of depression in older people [8–10]. Some of these diseases may bring about functional restrictions. So, physical problems may lead to depression by causing social isolation. Those elderly people with movement restrictions are especially at risk in this respect [8].

Osteoarthritis is the commonest type of arthritis in older people. Arthritis-related pain and depression are complex problems negatively affecting quality of life and physical functions [11]. Studies in the community have found elevated risks of depression among older people with chronic pain. The relationship between pain and depression is still poorly understood [11]. Depression and arthritis may be further linked through common inflammatory pathways, in which cytokines seem to play a major role [12]. In the case of the elderly with ochronosis, however, an association between disturbed tyrosine metabolism and depression having never been discussed in the literature, we speculate that activation of inflammatory pathways by HGA may cause a link between depression and ochronotic arthritis, or may be part of the explanation for this connection. Cytokines that are released in response to an activation of inflammatory pathways by HGA can enter the brain and then they may cause alterations of the metabolism of seroto-

nin and dopamine [13]. Future studies are required to explore the underlying mechanisms.

Until now, most studies have examined whether antidepressant treatments have a helpful effect on pain conditions. Unfortunately, no report has been found in the literature as to whether pain-relieving medications improve depressive symptoms. It has been reported that pain-relieving medications have little intrinsic antidepressant effect [14]. More research is needed to determine if alleviation of pain helps patients' depressive symptoms.

At the first application of the case to our clinic, it was thought that the patient's pains were related to ochronosis. The desired response could not be obtained despite the arrangement of treatment. Furthermore, the depressive symptoms described in the history were considered as secondary to the physical complaints. But, the response to the arranged treatment was not as good as expected and the depressive symptoms continued as before. Then, the patient was questioned for more details, and a decision was made for psychiatric consultation. In this consultation, the psychiatrist added an antidepressant (mirtazapine 15 mg/day) to the treatment regime. The patient was examined again after four weeks and it was decided to increase the dosages of mirtazapine (to 30 mg/day) and tramadole (to 100 mg/day).

In this case, we found that antidepressant treatment was as effective as the increased tramadole dosage on the marked reduction of pain. This pleiotropic effect of mirtazapine may develop by itself, or by increasing the activity of tramadole on neurons. In line with this, some biological evidence suggests that dysfunctional serotonergic and noradrenergic neurons could affect ascending and descending pathways, causing symptoms of depression and pain [15, 16].

Conclusions

It is important to bear in mind that prolonged and untreated pain in the elderly with ochronosis may cause depression. Depressive symptoms in ochronotic patients must not be overlooked by considering them as a normal part of the disease or of old age. Considering both of these factors, screening for depression in the

elderly population seems prudent. Identifying depression is important because these patients may be at risk of increased morbidity and mortality, although comprehensive data regarding outcomes is lacking. Future research is needed to test whether a care management approach integrating both ochronotic arthritis and depression treatments can produce additional health gains for older people with ochronotic arthritis and depression.

Acknowledgments

We had no financial support on this case study.

References

1. Smith RJ. Disorders of amino acid metabolism. In: Humes HD (ed.). *Kelley's textbook of internal medicine*, 4th ed. Philadelphia: Lippincott Williams & Wilkins 2000: 2788–2793.
2. Lin EH, Katon W, Von Korff M et al. Effect of improving depression care on pain and functional outcomes among older adults with arthritis: a randomized controlled trial. *JAMA* 2003; 290: 2428–2429.
3. Williams JW Jr, Katon W, Lin EH et al. The effectiveness of depression care management on diabetes-related outcomes in older patients. *Ann Intern Med* 2004; 140: 1015–1024.
4. Revell SI, Robinson JO, Rosen M et al. The reliability of a linear analogue for evaluating pain. *Anaesthesia* 1976; 31: 1191–1198.
5. van Marwijk HWJ, Wallace P, De Bock GH et al. Evaluation of the feasibility, reliability and diagnostic value of shortened versions of the geriatric depression scale. *Brit J Gen Pract* 1995; 45: 195–199.
6. *Diagnostic and statistical manual of mental disorders*. 4th ed, text revision. Washington: American Psychiatric Association 2000.
7. Felbor U, Mutsch Y, Grehn F et al. Ocular ochronosis in alkaptonuria patients carrying mutations in the homogentisate 1,2-dioxygenase gene. *Br J Ophthalmol* 1999; 83: 680–683.
8. Bisschop MI, Kriegsman DM, Deeg DJ et al. The longitudinal relation between chronic diseases and depression in older persons in the community: the longitudinal aging study Amsterdam. *J Clin Epidemiol* 2004; 57: 187–194.
9. Glasser M, Vogels L, Gravdal J. Geriatric depression assessment by rural primary care physicians. *Rural Remote Health* 2009; 9: 1180.
10. Almeida OP, Calver J, Jamrozik K et al. Obesity and metabolic syndrome increase the risk of incident depression in older men: the health in men study. *Am J Geriatr Psychiatry* 2009; 17: 889–898.
11. Jann MW, Slade JH. Antidepressant agents for the treatment of chronic pain and depression. *Pharmacotherapy* 2007; 27: 1571–1587.
12. Bruce TO. Comorbid depression in rheumatoid arthritis: pathophysiology and clinical implications. *Curr Psychiatry Rep* 2008; 10: 258–264.
13. Raison C, Capuron L, Miller A. Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends Immunol* 2006; 27: 24–31.
14. Bair MJ, Robinson RL, Katon W et al. Depression and pain comorbidity. *Arch Intern Med* 2003; 163: 2433–2445.
15. Talarowska-Bogusz M, Florkowski A, Radomska A et al. Depression and pain in arthrosis of spine and hip in elderly patients. *Pol Merkur Lekarski* 2006; 21: 566–569.
16. Stahl SM. Does depression hurt? *J Clin Psychiatry* 2002; 63: 273–274.

