Overviews

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89 years old, depression, pelvic fracture after falling, severe confusion: serotonergic syndrome

Differential diagnosis, importance of CYP450 and financial considerations

Case casuistry

Anna K.[1] had been referred to hospital care by her general practitioner due to exacerbations in her right leg. Anna had described increasingly immobilizing pain in her lower back, buttocks, and right leg up to the medial edge of her foot, and toes that had increased continuously during the past 6 days. There had been no previous

[1] **Translator Note:** Changed Frau K. to Anna to reflect cultural differences in English and to protect the patient's identity.

trauma, fall or heavy lifting. The pain intensity and its qualities could not be described. She had eaten less in the last few days. Her bowel movements were normal up to the day before going to the hospital; she was, however, more constipated. She stated not having urine or stool incontinence.

Social case history: Anna lived alone. Two times a day, she received support in the form of outpatient and meal services. Recently, she was registered in a nursing home since home treatment had become more difficult and more cumbersome. With reference to her cognitive skill, there was no history of incapacitation. Nevertheless, she had been treated for depression.

At hospitalization, the neurological status displayed symmetric sensitivity and normal strength in the lower extremities, except for dorsal extension in the foot and extension in the big toe (muscle strength grade M4). The perianal sensitivity and sphincter tone were preserved. The remaining status was normal. A fresh fracture was ruled out in the radiologic evaluation of the lumbar spine. Moderate to marked spondylarthrosis and concentrated coxarthrosis on the right side in case of mildly increased CRP (40 mg/L) were apparent. Anna was hospitalized for analgesic therapy and mobilization under the guidance of physical therapy. The hypokalemia detected upon admission was treated with potassium and magnesium. During her hospital stay, Anna fell approximately 50 cm to the floor in the evening of 12/24/2015. In this connection, she suffered a fracture of the inferior ramus of pubis on the left and an acetabulum fracture on the left.

The pain medication needed to be adapted since Anna complained of very strong immobilizing pain in her left pelvis. The pain medication with oxycodone (OxyContin) was expanded and switched to the continuous pain perfusor with pethidine (pethidine) and novamamine (Novalgin) due to an insufficient response. In addition, Anna received paracetamol (Dafalgan) i.v. and tolperisone (Mydocalm). p.o. A simple case of cystitis was nitrite positive in the urine status and the Uricult®, E. coli-sensitive to all common antibiotics and was treated bacteriostatically with a single 3 g dose of fosfomycin (Monuril).

During the course of treatment and based on this documentation (Table 1), the patient became delirious with symptoms of disorientation, hallucinations (monologues), and psychomotoric restlessness, such as fiddling and partial somnolence. The symptoms were more severely pronounced at night, in addition to

anxiety. The neuroleptic therapy with quetiapine was increased continuously and brought about a certain level of improvement. As a result, Anna became partially able to recall the names of family members. The CT (computer tomography) scan dated 12/28/2015 of the pelvis displayed, besides the acetabulum fracture on the left side, a dislocation of the lower fracture of the inferior ramus of pubis, left and an additional fracture of the sacral with no involvement of the neuroforamina (Ill. 1). Due to this complex situation, Anna was transferred to the Acute Geriatric Department for continued treatment.

When the patient was transferred to the Geriatric Department at 10 a.m. in the morning, her "delirious symptoms" stood formally in the foreground after having treated her pelvic ring fracture conservatively and her indicated "dementia development". The symptoms had started spontaneously on Day 1 after being hospitalized according to the existing clinical documentation. The symptoms fluctuated during the day and the night. The patient displayed an inability to follow a conversation or to follow what was said. In addition, her thoughts were disorganized. She seemed to be drowsy at intervals and could not be woken up and the CAM score criteria for a delirium were fulfilled. The CAM-S was performed to assess the severity of the delirium and with a score of 6 points, a severe delirium was the case. In formal terms, this was a severe, hypermotoric delirium.

<Insert image>
Ill. 1 Severe coxarthrosis, right; anterior acetabulum fracture, left; dislocated fracture of the inferior ramus of the pubis, left; fracture of the sacrum

A. Genetic results

	Gene	Genotype
Cytochrome	CYP1A2	*1A/*1F, heterozygous
	CYP2D6	*4/ *4, homozygous
	CYP2C19	*1/ *1, no variation
	CYP2B6	*1/*22, heterozygous
	CYP3A4	*1/ *1, no variation
	CYP3A5	*3/ *3, homozygous

Ill. 2 Results of the pharmacogenetic analysis

Clinically and neurologically, the patient was noticeably nervous and anxious. In reference to her muscular movements, she was very restless and shaky. Only slight reflexes were triggered when tapped lightly or the arms were touched. Her legs were constantly moving. In addition, she became unable to speak. Her speech was incomprehensible and incoherent.

Her eyeballs wandered while her pupils were normally dilated. In addition, the overall tone of all the extremities and a relatively rigid neck were also visible. The differential diagnoses displayed potential meningitis and a cerebral, ischemic or embolic event. However, neck stiffness was not very pronounced. No headaches, Brud Zinc or Kerning signs, or photophobia were observed. For an insulin event, no focal spots were indicated in the sense of paresis or motor weakness. All of her extremities moved spontaneously and vigorously. However, her movements were uncoordinated; her speech was not understandable. A CCT was very difficult to perform because of the patient's restlessness, but did not reveal a pathological focus. Performing a lumbar puncture or an MRI was not feasible in the current situation. The chest x-ray did not show any indications. Clinically, tachycardia and hypertension existed. The patient developed fever and diarrhea. The laboratory chemistry presented an electrolyte imbalance and an infection constellation in conjunction with an elevated CRP level of 97 mg/dL. The WBC count was 10,200. The BGA showed the image of non-compensated respiratory alkalosis in conjunction with tachypnea, tachycardia, and septic high temperatures.

Initially, the symptoms of serotonergic syndrome were compared with those of the serotonergic syndrome according to Sternberg [3–6]: autonomic dysfunction, neuromuscular signs, changes in cognitive levels and behavior in the presence of serotonergic medication. In this case, the patient's symptoms showed significantly more than the required 3 areas covered according to Sternberg. In addition, the serotonergic syndrome met the criteria of the "Hunter decision rules" [7, 8]. These criteria need to be positive in a minimum of one area and the patient was positive in 3 of them [2, 4, 5].

Diagnoses

- Strong suspected indication of moderate to severe serotonergic syndrome
- Hypermotoric delirium
- Possibly an arthritic recurrence in conjunction with concentrated coxarthrosis on the right side

- Primary chronic pain syndrome in the right leg and locomotion disorders
- Multifactorial fall (tolperisone, delirium, immobility)
- Secondary, acute severe pain syndrome in conjunction with the pelvic ring fracture
- Arterial hypertension

Following the patient's transfer to the Acute Geriatric Department, her pain treatment with pethidine was initially terminated and switched to a lower dosage of fentanyl (Durogesic® matrix) (12.5 μg) since fentanyl triggers or maintains serotonergic syndromes less or rarely based on relevant studies [7, 8]. All centrally active drugs, particularly mirtazapine (Mirtazapine), citalopram (Cipramil), quetiapine (Quetiapine), lorazepam (Lorazepam), and tolperisone (Mydocalm) were stopped. 5 mg of diazepanum (Diazepam) rectal were administered (multiple daily, as needed). In conjunction with increasing and septic high temperatures up to 39.4°, blood cultures were collected and physical cooling procedures were initiated. The dosage for cefepimum (Cefepime) was renally adjusted to 500 mg and administered 2 times intravenously. By adjusting the increasing retention parameters, the i.v. volume was replaced and the electrolytes balanced (hypernatremia (156 mmol/L), (hypokalemia (3 mmol/L). Multiple monitoring of the symptoms on a daily basis was defined.

The patient became somewhat quieter 24 h after stopping the medication. Her fever dropped after 48 h, she became alert and opened her eyes on purpose. She nevertheless developed strong inflammation parameters while maintaining a continued unclear focus (the blood cultures remained negative). Anna received an extended spectrum of antibiotics. Eighty hours after discontinuation, the serotonergic syndrome had almost completely resolved; she still fiddled a bit, yet the neurological symptoms had almost disappeared. She was slowly able to eat again after previously receiving peripheral venous nutrition (Smofkabiven peripher). The patient was able to speak again and communicate. She was focused, yet unable to remember. At this time, the depressive syndrome reappeared, which had been treated beforehand with mirtazapine and citalopram. Treatment with the medication was, however, not resumed since there had been negative reports in the literature and the recurrence of the serotonergic syndrome definitely had to be avoided. Mobilizing the patient in a wheelchair was also possible under pain therapy. Reorganizing care in a hospital bed was planned since the patient would not be to resume normal activities for another 6 weeks due to her pelvic fracture. From there, the further final therapy was planned.

The differential diagnosis [10–12] also foresaw a discussion on hyperthermia syndrome, which could be triggered by the administration of tolperisone, especially since the maximum dosage had been given, and several drugs simultaneously possessed a CYP2D6 affinity. However, it was not known which type of "metabolizer" the patient was. This was initially determined post-clinically (Fig. 2).

The anticholinergic syndrome disappeared since no tricyclic antidepressants or other anticholinergic agents had been used. The malignant neuroleptic syndrome also disappeared since one dose each of quetiapine and haloperidol had been administered, yet the symptomology showed no hyporeflexia, coma, or catatonia.

The medical history and pharmacological properties of the administered medications (including the elimination half-lives) [13, 14] showed that a serotonergic risk constellation existed. In conjunction with the patient's pronounced pain syndrome due to the complex pelvic ring fracture, she received a combined i.v. pain medication of pethidine 400 mg plus 2.5 g of metamizole with 2-4 ml/h. The total volume was continued with 400-800 mg pethidine and 2.5-5 g of metamizole i.v. In parallel, the patient's medication was continued with mirtazapine, citalopram, quetiapine, and lorazepam.

It has been pathophysiologically proven [15] that a longer term dosage of pethidine along with the accumulation of its active metabolite norpethidine leads to an inhibition of serotonin re-uptake from the synaptic gap.

Table 1 Clinical documentation (care) for transfer to the Acute Geriatrics Department (D = day)	
8:38 p.m.	Hospitalized, focused, clear, plagued by pain, partially mobile
10:12 p.m.	Development delirium along with restlessness, confusion
3:45 a.m.	Day/night reversal, confused, hypermotoric delirium
7:00 p.m.	Fell on the way to the bathroom, pelvic ring fracture
9:00 p.m.	Start of perfusor therapy with pethidine and Novalgin. Patient had deep sleep.
1:19 p.m.	General condition worse. Patient does not eat anymore, hardly any response.
2:03 p.m.	Patient in cold sweat
10:07 a.m.	Increased restlessness, hardly able to calm patient down
11:12 p.m.	Further motorical agitation, nervous, shaky
3:00 p.m.	Can no longer carry out any requests, mug fell out of patient's hand, reached into the air, fiddled around.
4:30 a.m.	Screamed, lashed out, communication no longer possible
4:35 a.m.	Ataxic spasms, whole body shook, tachycardia, rigors
10:00 a.m.	Transfer from the Orthopedic Department to the Acute Geriatric Department

Citalopram also acted as a selective serotonin reuptake inhibitor. These two substances resulted in significantly increased serotonin exposure in the synaptic gap. In addition, oxycodone may increase concentrations of serotonin release in broad areas of the forebrain and then trigger serotonergic syndrome together with citalopram. Other combinations resulting in serotonergic effects are possible [16].

Financial considerations of serotonergic syndrome in the DRG

Since serotonergic syndrome cannot be coded, it was difficult to adequately reverse the underlying efforts: staff costs (continuous, highly frequent care with 2 caregivers, 3 daily physician rounds, major involvement of senior physicians, multi-professional care, multiple disciplines including anesthetists, orthopedists, internal specialists, geriatricians, nutritionists), medical diagnosis (highly frequent laboratory checks, expensive diagnostics (procalcitonin, coagulation, CT skull), medical therapy (i.v. pain perfusor, i.v. administration of antibiotics, parenteral nutrition, multi-professional therapy concepts including physiotherapy, ergo therapy, activated therapeutic care, social work, neuropsychology).

The cost of the resulting costs might be estimated by a comparison calculation since there is a clinically close relationship to hypermotoric delirium, resp. parts of the serotonergic syndrome are classifiable this way. The cost structure of the hypermotoric delirium has already been published [17]. Hypermotoric deliriums last 1.4 days on average and cost approximately € 1,000 for staff and medication in personnel and material expenses in Germany. In the absence of a clinical model for serotonergic syndrome as a hypermotoric delirium (in this case for 9 days), the costs may be estimated as follows: the results are an estimated cost factor of € 6,400/CHF 19,200 for this serotonergic syndrome. To be added, however, are the costs of medication (i.v. pain therapy and treatment with antibiotics); technical laboratory (procalcitonin, blood cultures); and additional radiological diagnostics (CT skull) as they are considerably higher than in the case of a delirium patient.

The model calculation (Table 2) demonstrates that the financial costs for serotonergic syndrome are not covered in the DRG [diagnosis-related groups] system and ultimately require that the clinic assume the additional costs. It also nevertheless demonstrates that the interdisciplinary collaboration between the operative and geriatric departments created by the DRG can enable an improved course of treatment and also the coverage of these enormous additional costs. This effect is

particularly evident when the patient is monitored as early as possible by the acute geriatric department.

Discussion

Serotonergic syndrome is not rare; however, the precise incidence is unknown because many events go unrecognized. When SSRIs [serotonin reuptake inhibitors] are administered, adverse reactions or toxic effects are reported in 16–18% of cases. In a statistic dating back to 2002 and 2005 by the U.S. Poison Control Centers, poisonings with SSRIs were reported in 0.2% of deaths [18–20]. Antidepressants are by far the most commonly prescribed substances. The most commonly prescribed selective SSRI is citalopram, the defined daily doses (DDD) of which were 338.7 million in 2011. After citalopram, the psycho pharmaceutical mirtazapine is the second most frequent prescription with a DDD of 150.4 million in 2011 [21]. Treating and prescribing physicians must become aware of the associations between these agents and their hazards. This applies especially to the multi-morbid geriatric patients who often take more than 6 medications and very commonly prescribed antidepressants. Yet other antidepressants, such as sertraline or fluvoxamine, can lead to the induction of serotonergic syndrome [22, 23].

In this very elderly, geriatric patient population, pain is a common issue. The Drug Report 2012 [24] shows that the pain medications rank second of all prescriptions made. As such, the probability of being prescribed an opioid against pain and then experiencing serotonergic syndrome is significantly increased [25]. With this patient, severe degenerative changes in the right hip joint were possibly the cause of the pain in the right leg pain and the inflammatory syndrome.

The cause of her fall was multimodal. An important point is possibly the fact that the patient had received tolperisone (Mydocalm), a centrally acting muscle relaxant, upon admission. While the 450 mg dosage was correct, the substance was metabolized via CYP2D6, same as oxycodone and mirtazepine. CYP2D6 is part of the metabolic process of approximately every 4th medicine including many antidepressants, neuroleptics, β-adrenoceptor antagonists, anti-arrhythmic agents, antitussives and antiemetics. A genetic deficiency results in a dramatically slowed elimination from the body resulting in a relative overdose with accordingly increased side effects. CYP2D6 oxidizes and hydroxylizes certain substrates (pharmaceuticals) and activates (pro-drug) or deactivates these in the liver. The CYP2D6 may present as a "poor metabolizer" or an "ultra extensive metabolizer". In the first case, the

effects of the medications would increase. Determining the CYP2D6 activity in the patient confirmed that she was a "poor metabolizer", which explains the trigger for the serotonergic syndrome. It is thus possible that 450 mg may also be one dose and may be responsible for the patient's fall, restlessness, tremor, cold sweat, and temperature in spite of the medication's short half-life [26]. Another risk factor for a fall is when a delirium develops shortly after hospitalization.

Table 2 Model calculation

DRG	DRG	CMP	Revenue	Length of stay	Daily rate	Costs	Yield
G-DRG (LBFW € 3,232.73)	L63F	1.26	4,073.23	21	193	6,400	–2,326
With 8-550.1	L44Z	2.275	7,345.46	21	350	6,400	+945
With 8-550.1 Immed. to Geriatric Dept.	L44Z	2.275	δ[a] € +1,400	17	423	6,400	+2,345
Swiss DRG (Case Value CHF 10,000)	L638	1.2	12,000	21	571	19,20	–6,800
With 93.89.91	A95C	2.305	23,050	21	1,097	19,20	+3,850
With 93.89.91 Immed. to Geriatric Dept.	A95C	2.305	δ[b] CHF +6,120	17	1,355	19,20	+9,970

[a]δ yield of + €1,400 based on the calculation: loss of DRG yields at 0.7 CMP and 4 days of treatment (€ 1,200 plus effect of length of stay -4 days (€ 200) between 21 and 17 days of treatment)
[b]δ income of CHF +6,120 based on the calculation: loss of DRG yields at 0.7 CMP and 4 days of treatment ([CHF) 4,000] plus effect of length of stay -4 days (CHF 2,120) between 21 and 17 days of treatment)
LBFW = country-based case value

It was important that the diagnosis “delirium” had been made. It is a trigger diagnosis that opens the way into further investigation. Initially, it was the symptom constellation of ataxia, screaming, shakiness and psychomotor agitation that served the argument to transfer the "demented patient with delirium" to the Geriatrics Department. As it quickly turned out, the patient was not demented. Up to her hospitalization, she had been highly autonomous, relatively healthy, and was mentally fit. She had had a history of depression, which is why she was treated. In this case, it is surprising that the previous combination therapy of citalopram and

mirtazepine has not shown any side effects in relation to the serotonergic impact in this patient.

Two areas can rapidly lead treating physicians on the right track of serotonergic syndrome:

1. Verify additional neurological symptoms:
The neurological symptoms along with ataxia, tremors, excitability, clonus, hyperthermia, tachycardia, and tachypnea pave the way for serotonergic syndrome.

2. Verify the risk constellation in conjunction with the medication:
Previous medication treatment with an SSRI or an NAssA represents a clear risk factor for serotonergic side effects, particularly if an additional, fast effective pain medication becomes necessary as in this case.

Retrospectively, the symptoms of delirium documented in the 24 hours after hospitalization possibly already represented the onset of a very mild form of serotonergic. At this point in time, the patient had been given an additional type of medication described as a serotonin mixture in addition to citalopram and mirtazapinda [as illustrated in the literature [16].

In retrospect, the treatment had not developed in the right way until the patient received pethidine with an accumulation of norpethidine under continuous i.v. administration in very high doses. An account of this mechanism was also given in the literature [27].

The re-introduction of centrally acting drugs must be considered very carefully and critically to avoid a rapid resurgence of serotonergic syndrome [28]. Anna survived moderate to severe serotonin syndrome at 89 years of age, possibly only because of her healthy baseline state and her body's power of resistance.

The relationship of metabolizing the medication through CYP3A4 and CYP2D6 has shown how important such information might be for the pharmacologically defined activity of these two cytokines prior to initiating therapies with drugs in elderly patients. Whether a routine measurement of CYP activity is useful in elderly patients might be discussed.

In this case, the serotonergic syndrome lasted 9 days. The cost of serotonergic syndrome is dependent on the time point of diagnosis, condition and maintenance. If 9 days are used as the basis in a case like this one, then this serotonergic syndrome cost the clinic € 6,400, resp. CHF 19.200. This may result in a calculated under-coverage of a serotonergic case. Although the DRG system does not provide a direct illustration of serotonergic syndromes in the cost image matrix, it does provide a very important opportunity for the care of these patients, namely the financially evaluated interdisciplinary cooperation of departments in the treatment of geriatric patients. These positive characteristics of the DRG system would also need to be anchored more, in addition to the qualitative care, in the knowledge of treating physicians. The early, targeted management of such patients in skilled care, such as acute geriatrics, should be sought for prognostic and functional reasons.

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Compliance with ethical guidelines

Conflict of interest W. Weinrebe, A. Moutaouakil, K. Risz, M. Martin, K. Jeckelmann and
S. Goetz declare that a conflict of interest does not exist.

This article does not include any human or animal studies conducted by the authors. All patients that may be identified by photographic material or other information within the manuscript have given their written consent for this purpose.

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Literature