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ears old, depression, pelvic fracture fall, ere confusion: serotonergic syndrome

erential diagnosis, importance of CYP450 and financial siderations

casuistry

K.[1] had been referred to hospital care by her general practitioner due to exacerbations in ght leg. Anna had described increasingly immobilizing pain in her lower back, buttocks,

e: Changed Anna to Anna to reflect cultural differences in the English world and to protect the patient's name.

ight leg up to the medial edge of her foot, and toes that had increased continuously
g the past 6 days. There had been no previous trauma, fall or heavy lifting. The pain
sity and its qualities could not be described. She had eaten less in the last few days. Her
l movements were normal up to the day before going to the hospital; she was, however,
constipated. She stated not having urine or stool incontinence.

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

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

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

g the course of treatment and based on this documentation (Table 1), the patient became
ous with symptoms of disorientation, hallucinations (monologues), and psychomotoric
ssness, such as fiddling and partial somnolence. The symptoms were more severely

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

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

rt image>
Severe coxarthrosis, right; anterior acetabulum fracture, left; dislocated fracture of the
or ramus of the pubis, left; fracture of the sacrum

enetic results

	Gene	Genotype
chrome	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

Results of the pharmacogenetic analysis

cally and neurologically, the patient was noticeably nervous and anxious. Motorically, as very restless and shaky. Only slight reflexes were triggered when tapped lightly or ms were touched. Her legs were constantly moving. In addition, she became unable to . Her speech was incomprehensible and incoherent.

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

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

gnoses

trong suspected indication of moderate to severe serotonergic syndrome
ypermotoric delirium
ossibly an arthritic recurrence in conjunction with concentrated coxarthrosis on the right

de
rimary chronic pain syndrome in the right leg and locomotion disorders
[ultifactorial fall (tolperisone, delirium, immobility)
econdary, acute severe pain syndrome in conjunction with the pelvic ring fracture
rterial hypertension

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

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

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

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

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

been pathophysiologically proven [15] that a longer term dosage of pethidine along he accumulation of its active metabolite norpethidine leads to an inhibition of serotonin take from the synaptic gap.

e **1** Clinical documentation (care) for transfer to the Acute Geriatrics Department 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

›pram also acted as a selective serotonin reuptake inhibitor. These two substances ed in significantly increased serotonin exposure in the synaptic gap. In addition, ›done may increase concentrations of serotonin release in broad areas of the forebrain ıen trigger serotonergic syndrome together with citalopram. Other combinations ing in serotonergic effects are possible [16].

ncial considerations of serotonergic syndrome in the DRG

serotonergic syndrome cannot be coded, it was difficult to adequately reverse the lying efforts: staff costs (continuous, highly frequent care with 2 caregivers, 3 daily cian rounds, major involvement of senior physicians, multi-professional care, multiple ›lines including anesthetists, orthopedists, internal specialists, geriatricians, nutritionists), :al diagnosis (highly frequent laboratory checks, expensive diagnostics (procalcitonin, ılation, CT skull), medical therapy (i.v. pain perfusor, i.v. administration of antibiotics,

teral nutrition, multi-professional therapy concepts including physiotherapy, ergo therapy, activated therapeutic care, social , neuropsychology).

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

nodel calculation (Table 2) demonstrates that the financial costs for serotonergic ome are not covered in the DRG [diagnosis-related groups] system and ultimately re that the clinic assume the additional costs. It also nevertheless demonstrates that the lisciplinary collaboration between the operative and geriatric departments created by the can enable an improved course of treatment and also the coverage of these enormous onal costs. This effect is particularly evident when the patient is monitored as early as ble by the acute geriatric department.

ussion

onergic syndrome is not rare; however, the precise incidence is unknown because many s go unrecognized. When SSRIs [serotonin reuptake inhibitor] are administered, adverse ons or toxic effects are reported in 16–18% of cases. In a statistic dating back to 2002 005 by the U.S. Poison Control Centers, reported poisonings with SSRIs were reported % of deaths [18–20]. Antidepressants are by far the most commonly prescribed ances. The most commonly prescribed selective SSRI is citalopram, the defined daily (DDD) of which were 338.7 million in 2011. After citalopram, the psycho naceutical mirtazapine is the second most frequent prescription with a DDD of 150.4 n in 2011 [21]. Treating and prescribing physicians must become aware of the iations between these agents and their hazards. This applies especially to the multi-

id geriatric patients who often take more than 6 medications and very commonly prescribed antidepressants. Yet other epressants, such as sertraline or fluvoxamine, can lead to the induction of serotonergic ome [22, 23].

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

ause of her fall was multimodal. An important point is possibly the fact that the patient eceived tolperisone (Mydocalm), a centrally acting muscle relaxant, upon admission. e the 450 mg dosage was correct, the substance was metabolized via CYP2D6, same as odone and mirtazepine. CYP2D6 is part of the metabolic process of approximately every edicine including many antidepressants, neuroleptics, β-adrenoceptor antagonists, anti-thmic agents, antitussives and antiemetics. A genetic deficiency results in a dramatically d elimination from the body resulting in a relative overdose with accordingly increased ffects. CYP2D6 oxidizes and hydroxylizes certain substrates (pharmaceuticals) and ates (pro-drug) or deactivates these in the liver. The CYP2D6 may present as a "poor olizer" or an "ultra extensive metabolizer". In the first case, the effects of the cations would increase. Determining the CYP2D6 activity in the patient confirmed that as a "poor metabolizer", which explains the trigger for the serotonergic syndrome. It is possible that 450 mg may also be one dose and may be responsible for the patient's fall, ssness, tremor, cold sweat, and temperature in spite of the medication's short half-life Another risk factor for a fall is when a delirium develops shortly after hospitalization.

2 Model calculation

	DRG	CMP	Revenue	Length of stay	Daily rate	Costs	Yield
G	L63F	1.26	4,073.23	21	193	6,400	–2,326
W € 3,232.73)							
8-550.1	L44Z	2.275	7,345.46	21	350	6,400	+945
8-550.1	L44Z	2.275	δ[a]	17	423	6,400	+2,345
d. to Geriatric Dept.			€ +1,400				

DRG	L638	1.2	12,000	21	571	19,200	–6,80(
Value CHF 10,000)							
93.89.91	A95C	2.305	23,050	21	1,097	19,200	+3,85(
93.89.91	A95C	2.305	δ[b]	17	1,355	19,200	+9,97(
d. to Geriatric Dept.			CHF +6,120				

d of + €1,400 based on the calculation: loss of DRG yields at 0.7 CMP and 4 days of treatment (€ 1,200
fect of length of stay -4 days (€ 200) between 21 and 17 days of treatment)
me of CHF +6,120 based on the calculation: loss of DRG yields at 0.7 CMP and 4 days of treatment
) 4,000] plus effect of length of stay -4 days (CHF 2,120) between 21 and 17 days of treatment)
' = country-based case value

s important that the diagnosis delirium had been made. It is a trigger diagnosis that opens
ay into further investigation. Initially, it was the symptom constellation of ataxia,
ming, shakiness and psychomotor agitation that served the argument to transfer the
ented patient with delirium" to the Geriatrics Department. As it quickly turned out, the
nt was not demented. Up to her hospitalization, she had been highly autonomous,
vely healthy, and was mentally fit. She had had a history of depression, which is why she
reated. In this case, it is surprising that the previous combination therapy of citalopram
nirtazepine has not been shown any side effects in relation to the serotonergic impact in
atient.

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

rify additional neurological symptoms:
neurological symptoms along with ataxia, tremors, excitability, clonus, hyperthermia,
cardia, and tachypnea pave the way for serotonergic syndrome.

rify the risk constellation in conjunction with the medication:
ous medication treatment with an SSRI or an NAssA represents a clear risk factor for
onergic side effects, particularly if an additional, fast effective pain medication becomes
sary as in this case.

spectively, the symptoms of delirium documented in the 24 hours after hospitalization
bly already represented the onset of a very mild form of serotonergic. At this point in

the patient had been given an additional type of medication described as a serotonin mixture in addition to citalopram and zapinda [as illustrated in the literature [16].

rospect, the treatment had not developed in the right way until the patient received dline with an accumulation of norpethidine under continuous i.v. administration in very doses. This mechanism was also given an account of in the literature [27].

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

elationship of metabolizing the medication through CYP3A4 and CYP2D6 has shown mportant such information might be for the pharmacologically defined activity of these ytokines prior to initiating therapies with drugs in elderly patients. Whether a routine urement of CYP activity is useful in elderly patients might be discussed.

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

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ıpliance with ethical guidelines

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

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

rature