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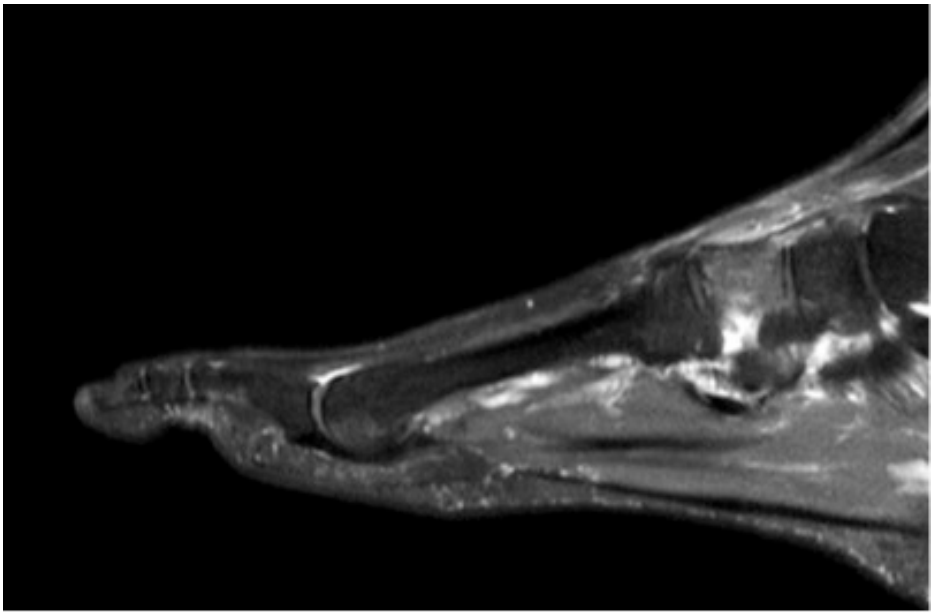

A patient with a painful foot; what is your diagnosis?

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Department of Internal Medicine
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3015 CE Rotterdam
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Tel.: +31 (0)10-703 59 54
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Van Zuiden Communications B.V.
PO Box 2122
2400 CC Alphen aan den Rijn
The Netherlands
Tel.: +31 (0)172-47 61 91
Email: mouton@vanzuidencommunications.nl
Internet: www.njm-online.nl

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EDITORIAL

Individualised decision-making

R.L. van Bruchem-Visser

Department of Internal Medicine and Geriatrics, Erasmus Medical Centre, Rotterdam, the Netherlands, tel.: +31 (0)10-4035979, email: r.l.visser@erasmusmc.nl

In their article, Berkhout-Byrne et al. report that the majority of older patients do not regret their decision to start dialysis. That being said, 7.4% of patients, however, did regret their choice. Especially the patients who felt they had not made the decision themselves, but had followed the advice of their nephrologist, showed remorse. Berkhout-Byrne concludes that it is of importance that decision-making is attuned to values and preferences of individual patients.[1]

I can think of no argument to contradict this statement. In an ideal world, the patient and the physician decide what to do in a joint operation. The professional provides the technical knowhow and explains the different options, and allows the patient to decide which road to take. By making the decision, the patient must consider his own preferences. Shared decision-making, instead of the professional telling the patient what to do.

However, taking into account the patient's values and preferences raises a number of questions.

Looking at the role of physicians: are we able to inform our patients about the technical aspects of an intervention in such a way that the patient fully understands, but while informing the patient, keep our own opinion out of it? In hindsight, regret can be felt about a certain decision. But nobody can tell what would have happened had that individual decided not to start with this specific treatment. It could be argued that perhaps other regrets would have emerged, with the inevitable physical symptoms that would have occurred in end-stage renal disease.

Secondly, how can one determine the values and preferences of each individual patient? Olthuis et al. wrote that the understanding of a patient's past, his lived experiences, will help in determining what is important to this specific patient. This could contribute to making medical decisions in a manner that is suitable for that unique patient.[2] This method of exploring lived experiences is not in our standard of care, particularly not in the outpatient clinic of a hospital. Should it be made a routine part of any workup for invasive treatments or procedures? If I look at my own patients, there are a number of patients with whom I have talked about their past life and wishes for the future. As a result, I have an insight of how this individual patient wants to shape his life for the future, how for example he would prefer to die. Knowing the background of a patient, having shared their previous experiences in a hospital or nursing home and being made privy of their beliefs about life and death enables me to understand their point of view. When a new disease appears, and treatment decisions must be made, I do inform them about all the technically possible treatment options. But, at the same time, I bear in mind their wishes. For instance, if I know a patient has had horrific experiences in the hospital and has declared a firm wish to renounce any surgical procedure, I will accept her refusal of surgery for colon carcinoma without feeling the need to convince her to reconsider. This is what she wants, as I have known for the last years. There is no need for me to try and persuade her to go against her own well-made decision.

Another interesting question is: where should the dialogue around values and preferences be initiated? In the hospital, with the nephrologist? Is the topic of said conversation directed only at the dialysis? And, for instance, will a cardiologist do exactly the same, only to change the topic of conversation to, for example, a TAVI procedure? Or should we strive towards a dialogue regarding preferences and wishes concerning treatment decisions in its broadest sense, without addressing a specific treatment or intervention? This conversation should, in my opinion, be started before a life-threatening illness arises because, as an Dutch saying goes: 'fear is a bad advisor'. Perhaps the office of the general practitioner is a far more suitable environment to explore the wishes of an individual patient.

Even when the values and preferences of a patient are investigated and recorded, it is very likely that beliefs and convictions will vary with the progression of life and illness. The topic of wishes concerning treatments and/or interventions should be revisited regularly, especially when changes in general health are apparent.

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ORIGINAL ARTICLE

Regret about the decision to start dialysis: a cross-sectional Dutch national survey

N. Berkhout-Byrne[1]*, A. Gaasbeek[1], M.J.K. Mallat[1], T.J. Rabelink[1], S.P. Mooijaart[3,4], F.W. Dekker[5], M. van Buren[1,2]

[1]Department of Nephrology, Leiden University Medical Centre, Leiden, the Netherlands, [2]Department of Nephrology, HAGA Hospital, The Hague, the Netherlands, [3]Department of Gerontology and Geriatrics, Leiden University Medical Centre, Leiden, the Netherlands, [4]Institute for Evidence-based Medicine in Old Age (IEMO), Leiden, the Netherlands, [5]Department of Clinical Epidemiology, Leiden University Medical Centre, Leiden, the Netherlands, *corresponding author: tel.: +31 (0)71-5299201 or +31 (0)71-5263754, fax: +31 (0)71-5266868, email: N.C.Berkhout-Byrne@LUMC.nl

ABSTRACT

Background: More older patients with end-stage renal disease (ESRD) are starting dialysis. Elderly patients often prefer treatments that focus on quality of life rather than primarily extending life and a substantial group of elderly dialysis patients might regret their decision to start dialysis. Healthcare provider and patient-related factors may be involved. Our objective was to measure the percentage of patients in the Netherlands who regretted their decision to start dialysis.

Methods: Cross-sectional Dutch national survey of dialysis patients. A short questionnaire about age, satisfaction with pre-dialysis education, present treatment, dialysis initiation, regret about decision to start dialysis and key figures in decision-making was developed.

Results: A total of 1371 questionnaires were returned for analysis from 28 dialysis units. Of the patients 7.4% regretted their decision to start dialysis, 50.5% reported the nephrologist's opinion to be crucial in decision-making and these patients experienced more regret than those who made the decision themselves (odds ratio, OR: 1.81). When family influenced decision-making more regret was experienced compared with those who decided themselves (OR: 2.73). Older age was associated with less regret ($p = 0.02$) and higher treatment satisfaction ($p < 0.001$); 52.8% of participants described dialysis initiation as being sudden.

Conclusion: The majority of patients did not regret their decision to start dialysis. Older patients were more satisfied with their treatment and felt less regret. The nephrologist's and the family's opinion were directional in decision-making on ESRD treatment options and were associated with more regret, especially in younger patients.

KEYWORDS

Decision-making, dialysis, ESRD, regret, treatment satisfaction

INTRODUCTION

Worldwide the number of older patients with end-stage renal disease (ESRD) starting dialysis is rising. In the Netherlands, 6463 patients were on dialysis in January 2015, 62% of whom were ≥ 65 years and within this group 37% were ≥ 75 years (for details *see Appendix, table 1*). Dialysis is associated with a high physical and psychosocial burden and limited survival, particularly for older patients with multi-morbidity.[1-3] Because of this many older patients prefer treatments that focus on quality of life (QOL) rather than primarily extending life with patient's personal values and perceptions playing an important role in the decision-making process.[4,5]

In the Netherlands multidisciplinary pre-dialysis care is formally established and its implementation monitored by certification.[6] Information on treatment options for ESRD encompasses a conservative care treatment option with a significant percentage of patients choosing not to undergo dialysis.[7] Early referral,[8-10] comprehensive pre-dialysis education, a planned start to dialysis and shared decision-making are cornerstones of pre-dialysis treatment and are in alignment with recommendations made by the Renal Physicians Association and the 'Choosing Wisely' campaign in the US.[11] Some studies have shown that an unplanned or sudden start to dialysis negated the benefits of early referral[12,13] whilst QOL improved and depression decreased when dialysis initiation was

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planned.[14] A number of surveys have shown that patients on dialysis felt they did not receive enough information to be able to make an informed decision.[15-21]

In a Canadian study, 61% of 584 dialysis patients regretted their decision to start dialysis over conservative care.[5] In their study the decision-making process reflected preferences of physicians and family members rather than the patient's personal choice, which could be one of the reasons for this alarmingly high regret rate. In contrast, in a recent survey of 128 US haemodialysis patients it was found that only 7% of participants regretted the decision to start dialysis even though 50% of patients reported that their nephrology provider was the person who most influenced their decision.[22]

Regret about decisions is a complex emotion which occurs in many different situations, is multifaceted (see *Appendix, table 2,* for an explanation on regret) and the second most frequently cited emotion after anxiety.[23] Shared decision-making has the potential to limit decisional regret and is defined as *'an approach where clinicians and patients share the best available evidence when faced with the task of making decisions, and where patients are supported to consider options, to achieve informed preferences'*.[24] This begs the question how to ensure that treatment choice is a true reflection of the patient's personal preferences and values so that patients experience less regret and more satisfaction with the choices they have made.

Given the structured information trajectory on ESRD treatment options in the Netherlands, which annihilates large differences between healthcare providers, we explored patient experience on treatment choice. Our aim was to measure the percentage of patients in the Netherlands who regretted their decision to start dialysis and to establish whether factors such as satisfaction with the treatment, whose opinion was crucial in the decision-making process, acute dialysis initiation, age and gender, were related to regret.

METHOD

As part of a quality of care initiative a short questionnaire was developed and included characteristics such as age, gender, dialysis vintage, satisfaction with pre-dialysis education, dialysis modality, planned or acute dialysis initiation (for questionnaire see *Appendix, table 3*). Other key elements incorporated into the questionnaire included satisfaction with treatment, regretting the decision to start dialysis and participants taking part in the decision-making process. The questionnaire was pilot-tested on a convenience sample of dialysis patients (face validity). After revision, re-testing the questionnaire was carried out to ensure ease of completion, clarity of questions and response options. Content validity assessment was established by a panel of experts (nephrologists, geriatricians, nurse practitioners, dialysis nurses). An assessment of appropriateness of wording and clarity was also requested. In general the questionnaire took 10 minutes to complete.

Dialysis patients ≥ 18 years of age, who were cognitively able to complete the questionnaire in Dutch, could participate. An e-mail was sent to all Dutch dialysis units inviting them to participate. Each participating centre approached their dialysis patients. The anonymous questionnaire was distributed between 25 May and 1 October 2014. The medical ethics committee of Leiden University Medical Centre exempted the study from the need for approval. The fact that patients completed and sent back the questionnaire, after being informed of the purpose and scope of the survey, was considered equivalent to informed consent. Following analysis each centre received a report with their results.

The eight-item questionnaire contained topics that are an integral part of the pre-dialysis decision-making process. Satisfaction with pre-dialysis information was measured using a five-point scale where '1' means 'completely disagree' and '5' means 'completely agree'. For the question about whose opinion was most influential in the decision-making process, five options were given: the nephrologist, nursing staff, myself, my family or friends, others. Satisfaction with the present dialysis treatment was measured using a six-point scale where '0' means 'very satisfied' and '6' means 'very dissatisfied'. Regret about the decision to start dialysis treatment was measured using a six-point scale where '0' means 'absolutely no regret' and '6' means 'very much regret'.

The qualitative data, transcripts of 206 remarks, were analysed systematically by thematic analysis. Two nephrology nurse practitioners, a nephrologist and two psychologists with experience in the field of nephrology were asked, via an open coding method, to code and categorise the remarks. Then main themes and sub-themes were identified, after which consensus was reached about the themes. In this qualitative analysis the patient comments took priority over the actual score on regret and therefore the reason for regret cannot be directly linked one to one to the score.

Statistical analysis

Scale (continuous) variables are given as mean ± standard deviation (SD). Categorical (nominal and ordinal) characteristics are shown as numbers and percentages. Association between discrete ordinal variables with less than five categories was analysed using cross-tables with Pearson's chi-square or Fisher's exact test, when appropriate. In case of correlation between ordinal variables with more than four categories and/or discrete scale variables Kendall's tau-b was calculated. Differences of means between multiple groups were analysed using one-way analysis of variance (ANOVA) and post-hoc testing according to Tukey's honest significance test. To predict the

association of the impact of whose opinion was important for the occurrence of regret, binary logistic regression was used. In a multivariate model we adjusted for possible confounding effects for age and gender on this association. The same procedure was used for the analysis of the relationship between occurrence of regret and sufficient pre-dialysis information, and separately between regret and satisfaction with dialysis treatment. Probabilities for each decision-making category and age group were calculated and plotted. P-values < 0.05 were considered statistically significant. All analyses were performed using IBM SPSS Statistics package, version 20.

RESULTS

We approached all 66 national dialysis units and 28 of these Dutch dialysis units (42%) participated in the survey. In total 2624 questionnaires were sent by post to the different dialysis units and 1371 were returned for the final analysis (52% response).

All participants in this survey were on haemodialysis or peritoneal dialysis, 64.5% of whom were ≥ 65 years. In-centre haemodialysis was the dominant form of dialysis (88.7%) (*table 1*). The results were representative for the Netherlands and compared well with those from

Table 1. *Baseline characteristics and questionnaire*

		n=1371	%
Age [#1]	<30 years	26	1.9
	30-39 years	56	4.1
	40-49 years	96	7.1
	50-59 years	167	12.3
	60-69 years	298	22.0
	70-79 years	404	29.8
	≥80 years	307	22.7
Gender[#2]	Male	793	58.4
	Female	564	41.6
Dialysis vintage[#3]	<1 year	345	26.6
	>1 year,<2 years	238	18.3
	>2 years,<5 years	411	31.6
	>5 years	305	23.5
Dialysis modality[#4]	Haemodialysis	1206	88.7
	Peritoneal dialysis	154	11.3
Place of dialysis[#5]	Hospital	1142	84.0
	Home	217	16.0
Sudden start of dialysis[#6]	Yes	697	52.8
	No	623	47.2
Sufficient pre-dialysis information to be able to make a decision[#7]	Completely disagree	65	4.8
	Disagree	35	2.6
	Neutral	132	9.7
	Agree	560	41.4
	Completely agree	562	41.5
Whose opinion was most important in pre-dialysis decision making? [#8]	Nephrologist	668	50.5
	Nurse	62	4.7
	Myself	409	30.9
	Family/friends	49	3.7
	Others	136	10.2
Satisfaction with present dialysis treatment[#9]	Very dissatisfied	8	0.6
	Dissatisfied	18	1.3
	Neutral	69	5.0
	Satisfied	540	39.6
	Very satisfied	731	53.5
Regret decision to dialyse[#10]	Very much regret	31	2.4
	Regret	67	5.0
	Neutral	72	5.4
	No regret	221	16.6
	Absolutely no regret	938	70.6

[#1] 17 missing; [#2] 14 missing; [#3] 72 missing; [#4] 11 missing; [#5] 12 missing; [#6] 51 missing; [#7] 17 missing; [#8] 47 missing; [#9] 5 missing; [#10] 42 missing.

Table 2. *Association of regret with key figures in decision-making and age**

		Crude (univariate)			Multivariable (adjusted)		
		OR	**CI**	**P-value**	**OR**	**CI**	**P-value**
Age (per 10 years)#		0.85	0.75-0.97	0.02	0.82	0.71-0.94	0.004
Gender	**Male vs Female**	**1.10**	**0.72-1.68**	**0.66**	**1.07**	**0.69-1.66**	**0.76**
Whose opinion is important in decision making	Myself	1.00					
	Nephrologist	1.49	0.90-2.48	0.12	1.81	1.07-3.06	0.03
	Nurse	0.28	0.04-2.11	0.22	0.33	0.04-2.52	0.29
	Family/friend	2.42	0.93-6.28	0.07	2.73	1.03-7.18	0.04
	Other	1.09	0.48-2.51	0.84	1.32	0.57-3.07	0.52

*Binary logistic model; OR = odds ratio; CI = 95% confidence interval.

the RENINE registry (**Re**gistratie **ni**erfunctievervanging **Ne**derland) (for details *see Appendix, table 1*).

Of 1329 respondents (42 missing), 7.4% reported regretting their decision to start dialysis (*table 1, Appendix table 3*). Older age was associated with less regret (Kendall's tau-b: -0.06, p = 0.011) and higher treatment satisfaction (Kendall's tau-b: 0.12, p < 0.001). In comparison with the very old patients (> 80 years), younger patients (< 30 years) had a higher risk for regret and the odds ratio for regret with the decision to dialyse decreased (on average) by 18% with the increase of age per decade (odds ratio: OR: 0.82, [confidence interval: 95% CI, 0.71 to 0.94]) (*table 2, figure 1*) and, moreover, the younger the patient the more regret experienced (< 50 years versus 50-69 years: OR: 1.66, [95% CI, 0.89 to 3.09], p = 0.108; < 50 years versus > 70 years: OR: 2.05, [95% CI, 1.13 to 3.72], p = 0.019; 50-69 years versus > 70 years: OR: 1.23, [95% CI, 0.76 to 2.00], p = 0.399).

Overall 50.5% of the patients reported the nephrologist's opinion to be crucial in the decision-making process (*table 1*). When the role of the nephrologist was the most important in decision-making, patients experienced more regret compared with patients who reported that they had made the decision themselves (adjusted for age and gender, OR: 1.81, [95% CI, 1.07 to 3.06]) (*table 2, figure 1*).

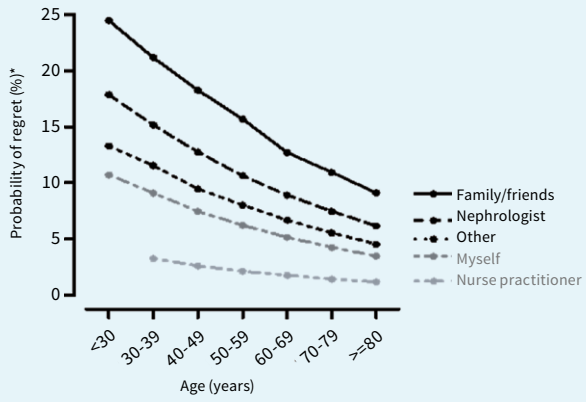
A small number of patients (3.7%) reported that family or friends played an important role in decision-making and when the role of the family was important, the OR for regret was found to be higher (OR: 2.73, [95% CI, 1.03 to 7.18]) (*table 2, figure 1*) and significance was reached (p = 0.04).

Overall 30.9% of the participants reported that they themselves were most important in the decision to start dialysis (*table 1*). Patients who reported that it was primarily their own decision to start dialysis were younger particularly in comparison to those whose decision was influenced by the nephrologist (63.8 ± 16.65 versus 70.0 ± 13.05, p < 0.001). When making the decision to choose haemodialysis, peritoneal dialysis or no dialysis treatment, 4.7% of participants reported that their nurse was important and 10.2% reported others as key figures in decision-making (family, doctor, peers etc.) (*tables 1 and 2, figure 1*).

There seemed to be a strong relationship between both sufficient pre-dialysis information to be able to partake in the decision-making process and satisfaction with dialysis treatment and regret. Participants who did not receive sufficient information had a higher risk for regret (complete disagreement, OR: 3.14, [95% CI, 1.34 to 7.38]), p = 0.009 (*table 3a*). Likewise participants who were dissatisfied with dialysis treatment had a higher risk for regret (dissatisfied, OR: 6.09, [95% CI, 1.83 to 20.21]), p = 0.003, (*table 3b*).

Overall 52.8% of the participants described dialysis initiation as sudden with the lowest reported percentage of sudden starts at 36.5% and the highest at 81.8% (*table 1*). This high percentage of sudden starts warranted further investigation. Of the 28 centres, 12 returned information about their percentages of medical urgent starts in 2014.

Figure 1. *Association of regret with age and key figures in decision-making*



* Effect of patient age and 'who influences decision making' on the probability of regret. Estimated from a binary logistic regression model.

Table 3a. *Association of regret with sufficient pre-dialysis information*

	OR (UV)	CI	P-value	OR (MV)	CI	P-value
Age (per 10 years)	0.85	0.75-0.97	0.02	0.88	0.77-1.00	0.051
Gender male vs female	1.10	0.72-1.68	0.66	1.11	0.72-1.71	0.632
Completely agree	1.0			1.0		
Agree	2.06	1.24-3.42	0.005	2.00	1.20-3.34	0.008
Neutral	2.68	1.34-5.34	0.005	2.61	1.31-5.20.	0.007
Disagree	2.06	0.59-7.21	0.25	2.09	0.60-7.34	0.250
Completely disagree	3.74	1.65-8.45	0.002	3.14	1.34-7.38	0.009

Table 3b. *Association of regret with satisfaction with dialysis treatment*

	OR (UV)	CI	P-value	OR (MV)	CI	P-value
Age per 10 years	0.85	0.75-0.97	0.02	0.90	0.78-1.02	0.106
Gender male vs female	1.10	0.72-1.68	0.66	1.06	0.69-1.63	0.789
Very satisfied	1.0			1.0		
Satisfied	2.13	1.34-3.38	0.001	2.04	1.28-3.25	0.003
Neutral	4.62	2.25-9.48	<0.0005	4.28	2.07-8.84	<0.0005
Dissatisfied	8.15	2.74-24.25	<0.0005	6.09	1.83-20.21	0.003
Very dissatisfied	4.24	0.48-37.34	0.19	5.24	0.57-48.58	0.145

OR = odds ratio; UV = univariate; CI = 95% confidence interval; (MV) = multivariate (adjusted)

These returned figures were below the 52.8% reported by participants in our survey with the lowest medical urgent start rate reported by participating centres at 7.40% and the highest at 39.4%.

No association was found between regret and dialysis modality (p = 0.68), regret and place of dialysis (home versus in-centre) (p = 0.83), or regret and acute start of dialysis (p = 0.19). No differences were found in gender and dialysis vintage between patients who regretted their decision to be treated with dialysis compared with those who did not regret their decision.

Patient comments about regret

Of the 1371 returned surveys, 1329 patients answered the question about regret (42 missing). Of this group 139 patients (10.5%) commented on their answer and reported regret due to a limited choice/no choice (55%), lack of information (11%), unfavourable side effects of dialysis (20 %), or other reasons, for example, no other alternative (14%). A further 67 patients (32.5%) reported no regret but did, however, comment on this question (*table 4*).

DISCUSSION

The main result of this survey was that of all the dialysis patients, 7.4% regretted the decision to start dialysis while the very old experienced less regret than younger patients. The results revealed that the nephrologist's and family's influence on decision-making was associated with more regret, particularly in younger patients and over 50% of patients reported dialysis initiation as being sudden. Furthermore, the results uncovered a number of reasons why patients experience regret. These findings highlight important factors in decision-making in the pre-dialysis phase and may add to limitation of decisional regret.

A limited number of participants regretted dialysis initiation and our results complement those of a recent survey in the US where 7% of patients regretted starting dialysis.[22] Results from both our study and the US study are in stark contrast to the high regret rate (61%) found in the Canadian study.[5] In our survey older age was found to be associated with less regret and higher treatment satisfaction, which is surprising as many elderly patients

Table 4. *Themes and sub-themes of patient comments on regret question*

Theme	Sub-theme	Examples of patients comments
No regret		I have no regret, however it is very tiring and sometimes I really don't want to go. Anyway! Once I've been, I say to myself ha, ha, survived another day. I have little/no regret that I choose home dialysis, because I have more freedom than in hospital. Of course there are days that you would rather not have to dialyse. But in the end you don't really have a choice. You can choose not to dialyse but you won't live long. Therefore for me the decision was easy and in the long run I'm satisfied with my choice and that's why I don't have regret.
Regret	• Process regret (lack of pre-dialysis information) • Option regret (experienced only when the outcome is unfavourable)* • Outcome regret (due to unfavourable outcomes)*	I'm very dissatisfied about the so called pre-dialysis (totally no pre-dialysis), I was thrown in at the deep end. I told my doctor about this (got no reaction). I was not given enough information about the consequences. I react badly to the treatment, sleep badly, no appetite, too tired to do anything. Walking has gotten worse, family life totally out of joint, exhausted, no energy to have visitors or to go visiting. Before I started treatment we went on holidays 2 or 3 times a year, we went in search of sunshine and we felt healthier and happier. Not positive message but I can't do anything about it. I don't feel happy and every week I dread those 3 days.
Regret: I had no choice	• It was the nephrologist's decision	I had to dialyse, it was nephrologist's advice, I had no symptoms, no pain etc. my kidneys were still active. I could pee independently, but still I had to start dialysis. There was very little discussion about the possibilities. They just said I had to dialyse. My opinion is, everything is already decided by the nephrologist what you have to do. I would have preferred to have more say in the matter.
	• Decision to dialyse was based on doing it for myself/others but the alternative is death;	If you want to live, for yourself, your family, then there is really no choice? It eases my mind to know that if I stop, I'll be dead within 2 weeks. If for one or other reason I don't want to continue I can end my life in this way. If I wasn't married I would never even have started.
	• No alternative, inevitability	Regret or not I had too, there wasn't much of a choice, we make the most of it.
Regret due to other reasons	Doubt about the regret question itself; negative emotions with this question.	Question 6 is a weird/ mean question for someone who has no choice whether to dialyse or not.

*These remarks are not only illustrative of patients emotions about the decision to dialyse but also reveal the complexity of the nature of regret. Regret can be experienced before (anticipated) or after the event (experienced), can have different targets (process, option, outcome) which can be experienced independently or in conjunction with each other (Joseph-Williams et al, 2011). For example if a patient with ESRD decides to dialyse and in the first few months on dialysis there are cannulation problems they might regret both the option and the outcome of their decision. However if after revision surgery of the fistula dialysis goes well, the patient may no longer regret the option and outcome of their choice.

are burdened by multiple comorbidities and are frail and because of this, are willing to trade a longer life expectancy for maintenance of QOL.[4,5] However, this relatively low level of regret could have been an underestimation as elderly patients (particularly those with cognitive impairment, frailty and multi-morbidity) might already have withdrawn from dialysis, indeed might not even have started dialysis.[25]

The majority of participants reported being satisfied with the present dialysis treatment. Taken together with the majority of patients who reported having received enough information to be able to participate in the decision-making process, the low regret rate suggests that pre-dialysis education in the Netherlands is indeed well and truly established. These findings are consistent with the results of a European survey carried out in 36 countries where patients reported being overall satisfied with information they received.[19] Similarly, in the US study 58% of patients described their quality of life as 'good' or 'very good' and 68% agreed they were prepared for dialysis.[22]

Although over 50% of the respondents reported the nephrologist as being important in decision-making, particularly older patients were satisfied and experienced less regret in this situation. Foote et al. demonstrated that older patients preferred their healthcare team to make decisions for them with patients regarding physician preferences as important.[26] Likewise in the US study, 50% of patients reported their nephrology care provider

as the most influential person in their decision to start dialysis.[22] The prominent role played by physicians in dialysis decision-making has been widely recognised,[17,27-29] with age, comorbidities, cognition, functional status, perceptions of QOL and patient or family request governing recommendations.[20,25,26,30] Therefore, the low rate of regret found in this survey, juxtaposed with the high influence of the nephrologist, begs the question whether physician influence should always necessarily be seen as undesired, particularly when the patient's subsequent satisfaction with dialysis is not negatively affected. On the basis of our results we advocate firstly the importance of recognising the different factors which influence individual decision-making where patient values and preferences are given prominence of place. Secondly the role of the nephrologist to be double-barrelled, not merely delivering information but importantly to follow through in facilitating a decision in the role, coined by Kurella as choice architects[21] hereby supporting and guiding each patient to a decision which befits their personal situation.

In contrast to older patients, it was found that younger patients had a higher risk for regret, especially when the nephrologist influenced decision-making. This result may suggest decisional conflict between younger patients and the nephrologist and importantly an unresolved decisional conflict is associated with experiencing regret and blaming providers.[31,32] Factors influencing patient involvement in shared decision-making include younger age, level of education, employment status and use of internet[28,33] with younger patients choosing options which increase the opportunity to find work or to remain employed.[29,33-36] Furthermore the higher regret rate in younger participants could be explained by disappointment regarding lack of transplantation options. These factors are therefore relevant and should be considered in the decision-making process.

Contrary to expectations, family members played only a minor role in the decision-making process (3.7%) which differs from a number of other studies,[5,29,36] but importantly when family were involved the chance of regret was found to be higher. Traditionally family members are seen as important participants in renal replacement therapy (RRT) modality choice[37] because of the profound impact on their own lives[4] and are therefore included in shared decision-making. Further research is needed to evaluate why 'doctor dominant' and 'family dominant' decisions rather than personal patient decisions are determinants of decisional regret.

Unravelling the reasons for regret and understanding its complexity is essential for improving shared decision-making. In this survey patients reported feeling regret because of lack of information, a limited or even no choice in the pre-dialysis phase, or because of unfavourable side effects of dialysis, which could be a form of delayed regret as the treatment gains its insidious grip on everyday life. Clearly some patients felt there was no other alternative, it was dialysis or death. The themes identified fit the model of regret proposed by Joseph-Williams et al.[23] and as such are modifiable. Information and education deficits prior to decision-making can be remitted by honest explanation of all the options including possible unfavourable consequences of dialysis for QOL. Actively encouraging patient involvement in decisions pertaining to RRT has the potential to limit decisional regret. Ambiguity was found between the reported experience of regret and the score on the regret scale, which indicates that all is not black and white and that many shades of grey surround the complex emotion of regret. Future research could help differentiate the source of experienced regret and interventions could be designed to minimise the risk of experiencing regret.

A major finding in this survey was the high percentage of participants who reported dialysis initiation as sudden (52.8%), which is remarkable given the high rate of satisfaction found alongside the reported high rate of information received prior to modality choice suggesting established pre-dialysis care and a planned start to dialysis. Our findings are in accordance with the results of the US study where 51% of patients reported starting dialysis in an acute hospital setting in spite of being prepared for dialysis.[22] Possible explanations include an unavoidable rapid decline of kidney function, late referral for education and counselling, patients own reluctance to start dialysis, delayed creation of vascular access and age discrimination in older patients with multi-morbid conditions. In the Netherlands, 'sudden' or 'urgent' start to dialysis is defined as dialysis initiation with less than six months of pre-dialysis care, with a catheter or as an inpatient. Planned dialysis initiation with vascular access is a marker of good practice. However, uncertainty about the course of each individual's illness trajectory and planning dialysis initiation is often difficult, even in early referred patients.[12] Furthermore, when care in the immediate months prior to RRT is inadequate the benefit of early referral can be lost if dialysis initiation is unplanned.[13] The high number of patients reporting a sudden start suggests that the transition period from pre-dialysis to actual RRT was perceived by patients as unexpected and in spite of adequate pre-dialysis care, patients can never truly be ready for such an invasive treatment.[4,28,38,39]

This survey set out primarily to inquire about the percentage of the Dutch dialysis population who regretted starting dialysis. There were several limitations to this survey, some of which are intrinsic to the use of

questionnaires. Possible confounding could have taken place by the questionnaire being completed in different places and in consultation with others. The findings were based on recollection and particulars in the pre-dialysis decision-making process and information about patients who declined to complete the survey or about economic status and education cannot be retained. The low rate of regret could have been due to healthier older patients choosing dialysis above conservative management or possibly non-motivated patients and those with additional physical and mental disabilities may have refused to participate in the survey or may not have been approached by the nurses. Despite these limitations, this was the first multicentre survey in Europe which measured the percentage of regret with the decision to dialyse, in spite of dialysis being a very disabling and invasive therapy. The return rate was high and because university hospitals, local community hospitals and satellite dialysis units participated, with diverse ethnic populations, results may be considered as representative for the Dutch dialysis population.

In conclusion, in this survey 7.4% regretted the decision to start dialysis and the very old experienced less regret than younger patients. More regret was experienced when the nephrologist and family were reported to play an important role in decision-making, particularly in younger patients and a number of reasons why patients experience regret were uncovered. A high percentage of respondents reported a sudden start to dialysis despite comprehensive pre-dialysis care. Our findings highlight the importance of decision-making being attuned to values and preferences of individual patients with specific attention being given to age related factors and significant others influencing shared decision-making.

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APPENDIX

Table 1. *Comparison of demographics of RENINE data and regret survey data*

	Regret survey (n = 1371)	%	RENINE (n = 6463)	%
≥ 65 years	885	64.55	4015	62.1
Haemodialysis (n =)	744	84.1	3513	87.5
Peritoneal dialysis (n =)	93	10.5	502	12.5
Missing	48			
Transplantation			998*	
Withdrawal from dialysis			102$	
Mortality on dialysis			1116#	
Mortality with a kidney transplant			282&	

RENINE: REgistratie NIerfunktievervanging Nederland; https://www.renine.nl/. Accessed February 2015
n = 6463, the total number of patients on dialysis on 1 January 2015
n = 1371: the total number of participants in the Regret survey
*Total number of kidney transplants (new) in 2014
$Total number of patients who withdrew from dialysis in 2014
#Total number of patients who died on dialysis in 2014
&Total number of patients who died with a kidney transplant in 2014

Table 2. *Illustration of the various types of regret**

A 78-year-old man with cardiovascular disease, diabetes mellitus type 2, is referred to the nephrologist because of a declining eGFR. Because the kidney function is below 20 ml/min he is referred on to the pre-dialysis multidisciplinary clinic for education and counselling alongside treatment of progression of the disease and its complications of CKD. He is now faced with the decision to opt for dialysis or a conservative supportive care pathway. He may experience **process regret** if he does not fully participate in the education process and therefore does not make an informed decision. He may experience **role regret** if he allows his family to make the decision for him. However, if he decides to dialyse and he can adjust to life on dialysis it will be unlikely that he experiences **option regret**. But if his symptoms of tiredness, itch, and polyneuropathy deteriorate he may subsequently experience **outcome regret**.

* Regret is an emotion that can occur in many different situations and is multi-faceted and, as demonstrated by Joseph-Williams et al., can be the result of action or inaction, anticipated or experienced, can be immediate or delayed, is not static and can follow a temporal pattern and can have both negative and positive outcomes.

Table 3. *Satisfaction with Dialysis Treatment Choice Questionnaire*

On which date did you fill out this form? _____

What is your age? _____

What is your gender? ☐ male ☐ female

1. **Do you agree with the following?**
   I received sufficient information to be involved in the decision to choose which type of dialysis suited me best.
   ☐ Completely disagree ☐ Disagree ☐ Neutral ☐ Agree ☐ Completely Agree

2. **Whose opinion was most important for you when making the decision to choose haemodialysis, peritoneal dialysis or no dialysis treatment?**
   ☐ My nephrologist
   ☐ My nurse
   ☐ Myself
   ☐ My family, partner, friend
   ☐ Other, e.g. _____

3. **When did you start dialysis?** _____

4. **Did you start dialysis suddenly?** ☐ Yes ☐ No

5. **What type of dialysis are you on now?**

Haemodialysis in hospital	☐ daytime	☐ in the night
Haemodialysis at home	☐ daytime	☐ in the night
Peritoneal dialysis	☐ (CAPD, day)	☐ (APD, night)

6. **How satisfied are you with your present dialysis treatment?**
   Very dissatisfied ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 Very satisfied

7. **Do you regret your decision to start dialysis?**
   Absolutely no regret ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 Very much regret

8. **Why do you regret starting dialysis?**
   _____

ORIGINAL ARTICLE

Prevalence of drug-drug interactions in the era of HIV integrase inhibitors: a retrospective clinical study

C. Baecke[1], I.C. Gyssens[1-3], L. Decoutere[4], J.C.H. van der Hilst[1,2], P. Messiaen[1,2]*

[1]Department of Infectious Diseases & Immunity, Jessa Hospital, Hasselt, Belgium, [2]BIOMED Research Institute, Hasselt University, Hasselt, Belgium, [3]Department of Internal Medicine, Radboud University Medical Center, Nijmegen, the Netherlands, [4]Department of Clinical Pharmacy, Jessa Hospital, Hasselt, Belgium, *corresponding author: tel.: +32 11309485, email: Peter.Messiaen@jessazh.be

ABSTRACT

Background: Antiretroviral agents pose a high risk for drug-drug interactions (DDIs), mainly but not limited to being a substrate, inducer or inhibitor of P450 cytochrome enzymes. In part metabolised by other pathways, integrase inhibitors might show a more favourable profile. The aim of this study was to investigate the prevalence of DDIs in daily clinical practice for patients starting different antiretroviral treatment (ART) regimens.

Methods: All patients starting ART in our centre from January 2009 to April 2016 were included. All prescribed co-medications since the start of ART were recorded retrospectively from the medical files and screened for DDIs using the Liverpool HIV drug interaction database. Only DDIs between antiretroviral and non-antiretroviral drugs were considered.

Results: We included 145 patients, of which 42% were on an integrase inhibitor-based regimen, mainly dolutegravir and elvitegravir. Of the patients, 78% (n = 113) took co-medication. Potential DDIs were seen in 63% of the patients with co-medication; contraindicated prescriptions were detected in 1%. Protease inhibitor-based ART was a risk factor for DDI (odds ratio (OR) 2.57; 95% confidence interval (CI) 1.06-6.19), in contrast to non-nucleoside reverse transcriptase inhibitor-based ART (OR 0.77; 95% CI 0.32-1.84). Concerning integrase inhibitors, a significantly lower risk was seen with dolutegravir-based treatment (OR 0.35; 95% CI 0.15-0.82), though not for elvitegravir-based ART (OR 2.51; 95% CI 0.66-9.58).

Conclusions: ART regimens pose a dissimilar risk for drug-drug interactions in clinical practice. Regarding the use of integrase inhibitors, a significantly lower risk was seen with dolutegravir-based treatment.

KEYWORDS

HIV integrase inhibitors, raltegravir, elvitegravir, dolutegravir, drug-drug interaction

INTRODUCTION

Antiretroviral agents pose a high risk for drug-drug interactions (DDIs) with other antiretroviral and non-antiretroviral drugs.[1] Protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTI) induce, inhibit, or are a substrate of cytochrome P450 enzymes. This is one of the major metabolic pathways potentially leading to an increased risk of toxicity or loss of efficacy of other antiretroviral and non-antiretroviral drugs.[2,3] Several studies have documented the main risk factors which increase the potential for DDIs in antiretroviral-treated patients: age, increasing comorbidities, number of co-medications used by patients and the use of (boosted) protease inhibitors in the antiretroviral treatment (ART) regimen.[4-9]

Inhibitors of the HIV-1 integrase are considered one of the most important recent advances in HIV treatment. Raltegravir, elvitegravir and dolutegravir are the integrase inhibitors which were – in chronological order – approved by the US Food and Drug Administration and the European Medicines Agency for use in antiretroviral-naïve as well as treatment-experienced patients.[10] They all have proven excellent results on virological efficacy, tolerability and safety,[11] and since recently are recommended as the preferred antiretroviral agents for initial therapy in most treatment guidelines for non-development countries.[12-14] Raltegravir is primarily metabolised through

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hepatic UGT1A1 glucuronidation and is not a substrate, inducer or inhibitor of the P450 cytochrome family.[15] Elvitegravir is metabolised predominantly by cytochrome P450 enzymes (CYP3A4) with minor pathways via UGT1A1/3-glucuronidation.[16] It needs a strong CYP3A4 inhibitor as pharmacokinetic enhancer for once-daily dosing. The booster used in the single tablet formulation with tenofovir/emtricitabine is cobicistat. Dolutegravir is predominantly metabolised by UGT1A1-mediated glucuronidation, but also by cytochrome P450 (CYP3A4) as minor pathway.[17,18]

The aim of this study was to investigate the prevalence of potential DDIs in daily clinical practice in a cohort of patients who started on different antiretroviral treatment regimens.

MATERIALS & METHODS

The study population comprised all patients starting ART in a single HIV clinic from January 2009 to April 2016. Retrospectively, data on ART (regimen choice, reasons for choice, starting date), CD4 T-cell nadir, virological treatment outcome and relevant comorbidities such as tuberculosis, active hepatitis B or C virus infection, were recorded from the medical files. If ART was later switched to another regimen, the investigation period was limited to the duration of the first prescribed ART regimen. All prescribed non-antiretroviral co-medications during this timeframe were recorded, including prescriptions started before the initiation of ART, which were continued during ART. Prescriptions by the general practitioner were also recorded in the files. The full medication list was not recorded during every patient visit, but at least once a year. The complete treatment of that period was subsequently screened for DDIs using the most recent version of the University of Liverpool HIV drug interaction database.[19] This database presents charts to determine the risk of DDIs between antiretroviral drugs as well as between antiretroviral and non-antiretroviral drugs. It is regularly updated, including data for the newest antiretroviral agents. The severity of an interaction is signalled in codes: orange code for a potential interaction that might require dosage modification or close monitoring to minimise clinical consequences, a red code for contraindicated co-administration of drugs, potentially leading to serious adverse events or an impaired efficacy, and a green code in the absence of anticipated interaction. Only DDIs between antiretroviral and non-antiretroviral drugs were taken into account in the study. Approval of the local ethics committee was obtained.

Statistical analysis was performed with SPSS 24. Student's t-test was used to determine differences in continuous variables between subgroups. The differences between other parameters were evaluated with Fisher's exact test. A multivariate logistic regression analysis was performed to determine independent risk factors for DDIs.

RESULTS

A total of 145 patients were included. Median age was 42 years (interquartile range 35-51 years) and 75% were male (*table 1*). An NNRTI-based regimen was used in 41 patients (28%), 44 (30%) were on a protease inhibitor-based regimen and 61 (42%) on an integrase inhibitor-based regimen. Dolutegravir (n = 42) and elvitegravir (n = 18) were the most prescribed integrase inhibitors. Raltegravir was prescribed to only one patient. Tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) was the most frequent NRTI backbone (n = 100), followed by abacavir/lamivudine (ABC/3TC) (n = 36) and zidovudine/lamivudine (n = 7). Two patients were on an NRTI-sparing regimen. Efavirenz (n = 21) and rilpivirine (n = 17) were the most prescribed NNRTIs; atazanavir (n = 27) and darunavir (n = 16) being the most prescribed protease inhibitors. In case of protease inhibitor-based therapy, ritonavir was used as pharmacological booster in 86% of cases, cobicistat in 11% of cases; one patient received unboosted atazanavir-based treatment. Four patients were receiving tuberculosis treatment during the study period. There was a low prevalence of active hepatitis B virus infection (n = 1; 0.7%) and hepatitis C virus co-infection was noted in nine patients (6.2%). Undetectable HIV viral load (< 50 copies HIV RNA/ml plasma) was achieved in 96% of all antiretroviral-treated patients at the end of the study period.

A total of 113 patients (78%) took co-medication during the investigated period, with a median of 4 drugs (range 1-18) per patient. Polypharmacy, defined as using ≥ 5 co-medications simultaneously, was seen in 26% of the patients, significantly correlated with age (p = 0.024). There were no differences in baseline characteristics and number of co-medications when comparing patient groups according to ART regimen. Antimicrobials were the most prescribed non-antiretroviral drug class (63%), followed by cardiovascular drugs (31%), central nervous system drugs (29%), vitamins and supplements (27%) and gastrointestinal drugs (25%) (*figure 1*). The exact start date of non-antiretroviral drugs could not be retrieved in 10.7% of the prescriptions, while 23.6% of the non-antiretroviral prescriptions predated the start of ART.

Potential DDIs were seen in 63% (n = 71) of the patients with co-medications and in almost one-third (160/503; 32%) of all non-antiretroviral prescriptions. Prescriptions predating ART resulted in a relatively higher prevalence of potential DDI compared with 'post-ART' prescriptions,

although not statistically significant (43.6% vs 35.0%, p = 0.129).

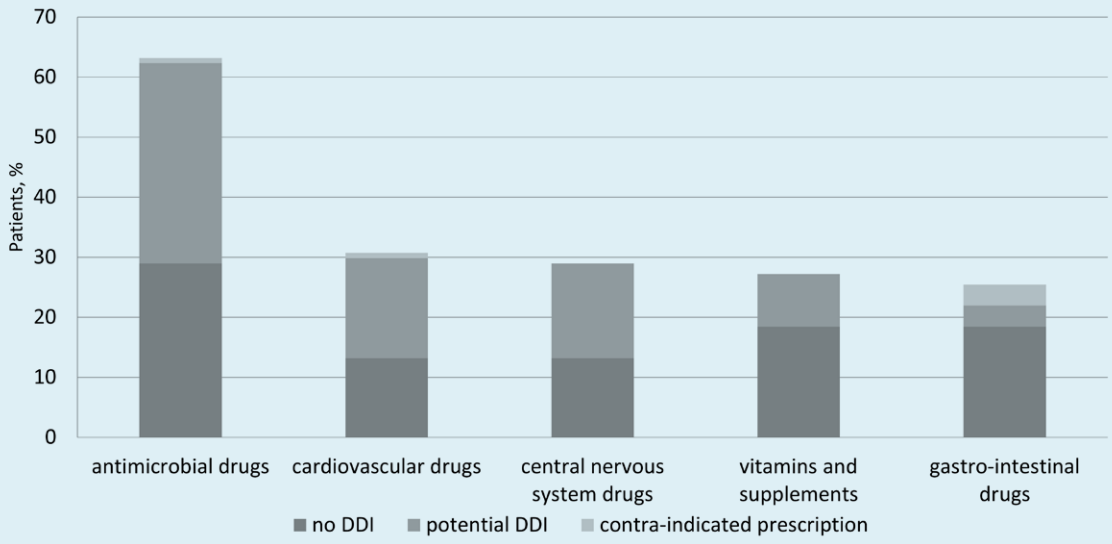
There were no significant differences in prevalence of potential DDIs when comparing the co-medication drug classes (*figure 1*). Concerning antimicrobial agents, potential DDIs most frequently involved sulfamethoxazole/trimethoprim, pentamidine and atovaquone/proguanil. The most frequent potential DDI with cardiovascular drugs was noted with amlodipine, bisoprolol and pravastatin. Potential DDIs with escitalopram and trazodone appeared most frequently in the central nervous system drug class. Amlodipine and trazodone are mainly CYP3A4 metabolised and can be strongly influenced by CYP3A inducers (nevirapine, efavirenz) or by CYP3A inhibitors (ritonavir, cobicistat). Drugs which are partially metabolised by CYP3A4 but also by other CYP enzyme families as CYP2D6 (bisoprolol) or CYP2C19 (escitalopram) can experience similar, more moderate effects. Other pathways included OATP1B1 (pravastatin) through inhibition by cobicistat boosted elvitegravir or induction by efavirenz.

Contraindicated prescriptions were detected in 1% (n = 6) of all co-medication use, involving disproportionally more gastrointestinal drugs and protease inhibitors, compared with the other drug classes (*figure 1*). Most of these interactions involved CYP3A4: ritonavir boosted atazanavir and CYP3A4 inhibition leading towards potentially increased domperidone exposure (n = 2); boosted atazanavir and rifampicin, where CYP3A4 induction could result in decreased atazanavir levels (n = 1); boosted elvitegravir inhibiting CYP3A4 and increasing the drug levels of lercanidipine (n = 1) and co-administration of ritonavir boosted atazanavir with proton pump inhibitors, potentially decreasing the effective atazanavir concentration due to decreased intra-gastric solubility (n = 1).

Avoidance of potential DDIs was mentioned as one of the reasons for choosing a dolutegravir-containing ART regimen in four patients: two patients with tuberculosis treatment, one patient with chemotherapy, and one patient receiving both. For the other patients on integrase inhibitor-based treatment (57/61, 93%), there was no indication that potential DDIs played a role in the regimen choice.

To determine the impact of choice of the third agent on the prevalence of DDIs, two subgroups were compared: patients with co-medication and potential DDIs and/or contraindicated prescriptions (n = 71) and patients with co-medication without DDIs (n = 42). Antiretroviral-treated patients with co-medication and DDIs trended towards older age, took significantly more co-medications and had a significantly lower CD4 T-cell nadir at the start of ART compared with those without DDIs (*table 1*). There was no difference in antiviral treatment outcome between the two groups. The prevalence of DDIs was significantly different according to the choice of backbone: patients with co-medication and DDIs more often used TDF/FTC, those without DDIs more frequently ABC/3TC, compared with the first group. The effect of the ART backbone itself on the individual prevalence for DDI was however weak:

Figure 1. *Co-medications used by antiretroviral-treated patients with at least one co-medication (n = 113)*



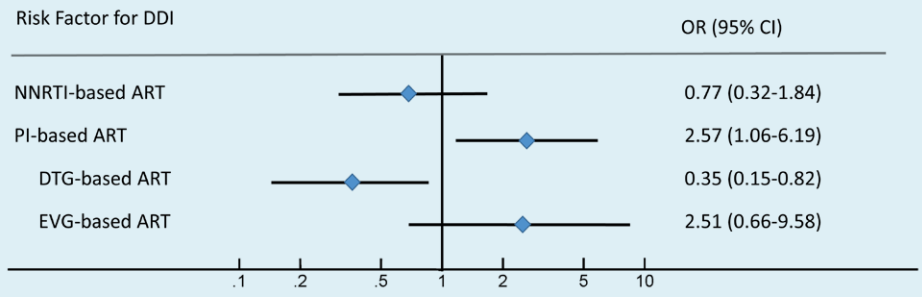
Percentage of patients using one or more drugs of indicated non-antiretroviral drug classes, subdivided in proportions of patients with contraindicated prescriptions (light grey), potential drug-drug interaction (grey) and without indication for drug-drug interaction (dark grey)
ART = antiretroviral treatment; DDI = drug-drug interaction

Table 1. *Patient characteristics*

Characteristics	All patients (n = 145)	Antiretroviral-treated patients with co-medication and DDI[a] (n = 71)	Antiretroviral-treated patients with co-medication without DDI[a] (n = 42)	P value[b]
Median age in years (IQR)	42 (35-51)	44 (37-51)	39 (33-50)	0.123
Male gender, n (%)	109 (75.2)	51 (71.8)	34 (81.0)	0.368
Median CD4+ T-cell nadir, cells/µl (IQR)	260 (135-360)	185 (55-282)	350 (150-420)	0.034
Start of ART before 2015, n (%)	91 (62.8)	47 (66.2)	27 (64.2)	0.519
Viral suppression < 50 copies/ml, n (%)	139 (95.9)	70 (98.6)	40 (95.2)	0.554
HBV coinfection (HBsAg-positive), n (%)	1 (0.7)	1 (1.4)	0 (0.0)	1.000
HCV coinfection, n (%)	9 (6.2)	5 (7.0)	3 (7.1)	1.000
TB treatment during study period, n (%)	4 (2.8)	4 (5.6)	0 (0.0)	0.295
Median number of non-ARV co-medication, n (IQR)	2 (1-5)	4 (2-8)	2 (1-4)	0.000
Polypharmacy, n (%)	38 (26.2)	31 (43.7)	7 (16.7)	0.004
Backbone				
TDF/FTC, n (%)	100 (69.0)	56 (78.9)	23 (54.8)	0.010
ABC/3TC, n (%)	36 (24.8)	12 (16.9)	16 (38.1)	0.014
AZT/3TC, n (%)	7 (4.8)	3 (4.2)	2 (4.8)	1.000
Third agent				
NNRTI, n (%)	41 (28.3)	17 (23.9)	12 (28.6)	0.658
Protease inhibitor, n (%)	44 (30.3)	28 (39.4)	9 (21.4)	0.062
Integrase inhibitor n (%)	61 (42.1)	26 (36.6)	21 (50)	0.174
Elvitegravir, n (%)	18 (12.4)	11 (15.5)	3 (7.1)	0.246
Dolutegravir, n (%)	42 (29.0)	15 (21.1)	17 (40.9)	0.033
Raltegravir, n (%)	1 (0.7)	0 (0.0)	1 (2.4)	1.000

[a]DDI comprises potential DDI + contraindicated prescriptions
[b]Antiretroviral-treated patients with co-medication and DDI vs those without DDI
IQR = interquartile range; ART = antiretroviral therapy; DDI = drug-drug interaction; HBV = hepatitis B virus; HCV = hepatitis C virus; TB = tuberculosis; TDF/FTC = tenofovir disoproxyl fumarate/emtricitabine; ABC/3TC = abacavir/lamivudine; AZT/3TC = zidovudine/lamivudine; NNRTI = non-nucleoside reverse transcriptase inhibitors.

Figure 2. *Third agent in ART as independent risk factor for drug-drug interaction*



Plot of the odds ratios (OR) of third agents in ART as risk factor for potential or contraindicated drug-drug interaction (DDI). Data based on the antiretroviral-treated patients with co-medication (n = 113) with omission of those patients where DDI was solely due to the backbone (n = 3)
The black vertical line indicates OR = 1, signifying no increased (right) or decreased (left) risk. 95% confidence intervals (CI) are indicated.
DDI = drug-drug interaction; OR = odds ratio; CI = confidence interval; ART = antiretroviral treatment; NNRTI = non-nucleoside reverse transcriptase inhibitors; PI = protease inhibitor; EVG = elvitegravir; DTG = dolutegravir.

in 22% and 19% of the patients treated with TDF/FTC or ABC/3TC, respectively, the NRTIs were involved in DDI. A more detailed analysis showed that DDIs were solely due to the backbone in only three patients: one patient on TDF/FTC + efavirenz and two patients on TDF/FTC + dolutegravir. Those patients were removed from the subsequent multivariate logistic regression analysis.

The logistic regression analysis showed that protease inhibitor-based ART was an independent risk factor for potential or contraindicated DDIs (odds ratio (OR) 2.57; 95% confidence interval (CI) 1.06-6.19) (*figure 2*). NNRTI-based ART was not associated with a higher risk (OR 0.77; 95% CI 0.32-1.84). A significantly lower risk for DDI was seen with dolutegravir-based treatment (OR 0.35; 95% CI 0.15-0.82), though not with elvitegravir-based ART (OR 2.51; 95% CI 0.66-9.58). Due to the small number of patients treated with raltegravir, the effect of this integrase inhibitor on the prevalence of DDIs could not be assessed.

DISCUSSION

This retrospective study aimed at investigating the prevalence of potential DDIs or contraindicated prescriptions in a real-life patient cohort and the relation with the choice of ART regimen, in view of the recent surge of integrase inhibitor use. Of the patients, 78% were prescribed co-medication during the investigation timeframe, which is in line with previously reported data.[6] The median CD4 cell count nadir at the start of ART was significantly lower in the patients with DDIs, suggesting a patient group with more late presenters or longer HIV infection history, potentially with more risk of comorbidities. There was, however, no difference in virological treatment outcome between the groups with and without DDIs. The prevalence of DDIs was lower in those patients using ABC/3TC, although the effect of the NRTI backbone itself is considered minimal: all NRTI backbones had an equally low contribution to the prevalence of DDIs. The frequent use of a single-tablet regimen containing ABC/3TC and dolutegravir could explain these findings. When considering the integrase inhibitors, dolutegravir-based treatment did show a significantly lower risk for DDI, which was not the case for elvitegravir. This correlates with the different routes of metabolisation of these drugs. The impact of raltegravir could not be assessed because of the low use in our clinic, partly due to drug registration regulations in Belgium. Previously published data showed the favourable characteristics of raltegravir concerning DDI prevalence in clinical practice.[8]

As non-antiretroviral prescriptions pre-dating the start of ART were also included in our analysis, we could expect a prescription bias concerning the choice of ART regimen. Remarkably, the smaller proportion of 'pre-ART' prescriptions (23.6% of the total non-antiretroviral prescriptions) resulted in a relatively higher potential for DDI, indicating there might have been more attention to potential DDIs when prescribing non-antiretroviral drugs in patients already on ART, compared with treatment-naïve patients starting ART. Avoidance of potential DDIs was mentioned in a limited number of patients starting dolutegravir, mainly related to oncological treatment or the concomitant use of anti-mycobacterial drugs.

It is important to mention the retrospective and single centre data collection as a limitation of this study as well as the lack of data on co-medication outcome and clinical toxicity. Furthermore, co-medication use might have been underreported or incompletely recorded leading to potential bias, especially the use of vitamins and mineral supplements and their potential interaction with integrase inhibitors.

In conclusion, our retrospective cohort study confirms the dissimilar risk of antiretroviral drugs for drug-drug interactions in clinical practice. Regarding the use of integrase inhibitors, a significantly lower risk was seen with dolutegravir-based treatment.

Part of this work was presented at the HIV Drug Therapy Congress in Glasgow in November 2016, Abstract P318 Messiaen P, Baecke C, van der Hilst J. *Prevalence of drug-drug interactions involving antiretroviral treatment: impact of the integrase inhibitor class.*

DISCLOSURES

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ORIGINAL ARTICLE

Elderly patients with an atypical presentation of illness in the emergency department

M.R. Hofman*, F. van den Hanenberg, I.N. Sierevelt, C.R. Tulner

Department of Geriatric Medicine, Medical Center Slotervaart, Amsterdam, the Netherlands,
*corresponding author: tel.: +31 (0)20-5129333, fax: +31 (0)20-5124252,
email: mariellehofman@hotmail.com

ABSTRACT

Background: Very little information is available on the prevalence and clinical outcome of elderly patients with atypical presentations of illness in the emergency department. The objective was to determine the prevalence and clinical outcome of elderly patients seen in the emergency department with an atypical presentation.
Methods: A monocentric retrospective observational study on 355 elderly patients presenting to the emergency department. Patients of 80 years and older were included. Data were extracted from the electronic medical file.
Results: A total of 355 patients were included, with a mean age of 86 years; 53% of these elderly patients had an atypical presentation of illness. Mostly this was due to a fall (71%). A total of 15% of the patients with an atypical presentation reported no specific symptoms of the underlying disease. Patients with atypical presentation were more likely to have a longer stay in hospital ($p < 0.001$), to be discharged to a care institution ($p = 0.000$), and to have a higher delirium observation score ($p < 0.001$). There was no significant difference in one-year survival ($p = 0.056$).
Conclusion: Atypical presentation of illness in elderly patients is highly prevalent in the emergency department. Falling accidents are the most important reason for this. Patients with an atypical presentation have a worse clinical outcome. Accurate training of emergency staff is necessary to recognise this group of patients to ensure proper clinical monitoring and timely treatment.

KEYWORDS

Atypical illness presentation, elderly patients, emergency department.

INTRODUCTION

Older patients are a growing demographic in our healthcare system. The emergency department is one of the places where this can be encountered. In the emergency department, 12 to 43% of the patients are elderly.[1-3] They visit the emergency department more frequently, with more urgent diseases, need more diagnostics and stay longer. Furthermore, they have a greater chance of being hospitalised and being misdiagnosed.[1,3-6] Atypical presentation of illness could be the cause of misdiagnosis.
Presentation with well-known and highly prevalent atypical symptoms (e.g. immobility, impaired cognition and incontinence) is often referred to as geriatric syndromes.[7]
There is no gold standard definition for an atypical presentation of illness. Common presentations include altered mental state, failure to eat and drink, failure to develop fever, lack of pain, functional decline, reduced mobility, falling, fatigue and urinary incontinence.[8]
Limpawattana et al. defined atypical illness presentation as patients with no signs and symptoms or unusual signs and symptoms, unrelated to or even the opposite of what is usually expected.
It is known that the geriatric population often have with an altered clinical presentation.[9,10] Moreover atypical presentation of illness seems to be an independent predictor of poor hospital outcome.[9,11] Early recognition and management of atypical presentation potentially results in positive health outcomes by prompting accurate diagnosis, reducing the risk of new comorbidities, reducing hospital length of stay, and improving quality of life.[12]
Since little research has been carried out in this area, we conducted a monocentric retrospective observational study on 355 elderly patients presenting to the emergency department. We investigated the prevalence and clinical

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outcome of atypical presentations of illness among elderly patients in order to assess the clinical relevance of this categorisation.

MATERIALS AND METHODS

Setting and design

This retrospective observational study was conducted in Medical Center Slotervaart, Amsterdam. This is a large urban teaching hospital with 310 beds. Approximately 14,000 patients are admitted to the emergency department per year. The study was approved by the Medical Ethics Committee of the MC Slotervaart.

Patients

All patients of 80 years and older admitted to the emergency department between 1 June 2013 and 7 May 2014 were eligible for study inclusion. We reduced the size of the group by including only patients who were admitted to the emergency department in the first seven days of every month during this study period.

Data collection

Data were extracted from the electronic patient data management system: age, gender, communication difficulties, living situation, amount of medication, use of psychoactive drugs, triage colour (red: in need of immediate medical attention, orange: in need of delayed medical attention, yellow: in need of minimum medical attention), subsequent hospitalisation, history of dementia or mild cognitive impairment (according DSM-IV-TR), main reason of admission, history of falling, new urine incontinence, functional decline and cognitive decline prior to admission, Charlson comorbidity index, highest delirium observation score, decubitus during hospitalisation, length of stay on the emergency department, length of stay in hospital, referral to a care institution, and date of death.

To obtain survival data at one year after admission, we contacted general practitioners and nursing homes.

Definition

If the anamnesis in the emergency department included the usual symptoms of the underlying disease, it was defined as a typical illness presentation. If the anamnesis in the emergency department revealed none of the symptoms known for the underlying disease (e.g. lack of fever, dysuria and frequency in case of urinary tract infection, or lack of fever, coughing and dyspnoea in case of pneumonia), and/or the presentation was preceded by a geriatric syndrome (falling, new urine incontinence, functional decline or cognitive decline) with a known or unknown cause, it was also defined as atypical illness presentation. There was a second assessor (FvdH) to independently assess all patients for type of presentation. When no agreement was reached, a third assessor (CT) defined the category.

Statistical analysis

Analyses were performed using SPSS version 23 (SPSS, Inc., Chicago, IL). Patients with missing data were excluded from the relevant analyses. Outcome variables were categorised into atypical and typical presentations of illness. The chi-squared test was used to compare univariate associations between categorical variables. The Student's t-test was used to compare continuous variables. For statistical comparison of the mean, the Mann-Whitney U test was used. For all tests a p-value of < 0.05 (two-tailed test) was considered to be significant. The interrater reliability for type of presentation was 0.92 (95% CI 0.87-0.96), evaluated with Cohen's kappa statistic.

RESULTS

A total of 355 patients were included. *Table 1* presents the baseline characteristics of the study population. The mean age was 86 years, and the proportion of female patients was 60%. Before admission 80% lived at home. A cognitive disorder was present in 30% and approximately the same number had communication problems. The median Charlson comorbidity index before admission was 2. Approximately half of the patients were triaged yellow. Neurological disease (15%), infectious disease (16%) and fracture (12%) were the most frequent causes of the visit to the emergency department.

In 53% of the patients there was an atypical presentation of the illness; 29 patients (15%) showed none of the usual symptoms for the underlying disease in the anamnesis. A cognitive disorder was present in 21 of these 29 patients without symptoms.

In 99% of the atypical presentations the patient had a geriatric syndrome, with falling by far the most frequent symptom (71%). New urine incontinence was seen in 3%, functional decline in 11% and cognitive decline in 29%. In 66% of these cases the cause of the geriatric syndrome was clear (*figure 1*).

Patients with atypical presentations were significantly older ($p = 0.000$), more often resided in a care institution ($p = 0.005$), had higher rates of cognitive disorders ($p = 0.001$) and more frequently experienced problems with communication ($p = 0.000$).

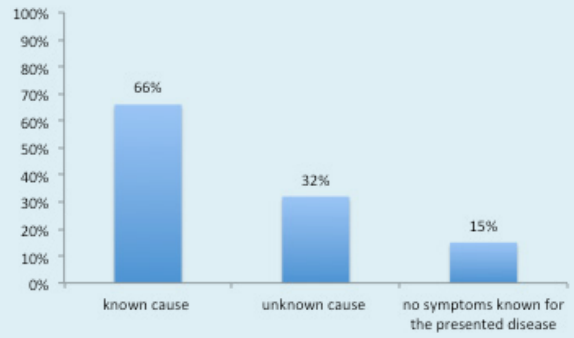
Compared with patients with a typical illness presentation, patients with an atypical presentation were more likely to have a longer stay in hospital ($p < 0.001$), to be discharged

Table 1. *Baseline characteristics of patients*

Characteristic	All patients (n = 355)	Typical presentation (n = 167)	Atypical presentation (n = 188)	p-value
Age (years), mean (SD)	85.7 (4.3)	84.9 (3.4)	86.5 (4.8)	0.000
Gender, n (%)				0.06
Female	212 (60)	91 (55)	121 (64)	
Male	143 (40)	76 (46)	67 (36)	
Living situation, n (%)				**0.005**
Home	281 (80)	142 (86)	139 (74)	
Care institution[2]	72 (20)	23 (14)	49 (26)	
Missing	((2))			
Cognitive disorder[3], n (%))	106 (30)	35 (21)	71 (38)	0.001
Triage colour, n (%)				**0.18**
Orange/red[1]	50 (15)	29 (19)	21 (12)	
Yellow	160 (48)	69 (44)	91 (51)	
Green	126 (38)	58 (37)	68 (38)	
Charlson comorbidity index[4], median (IQR)	2 (1-3)	2 (1-3)	1 (1-3)	0.039
Admission diagnosis, n (%)				
Fracture	41 (12)	1 (1)	40 (21)	0.000
Gastrointestinal	36 (10)	30 (18)	6 (3)	
Malignancy	6 (2)	5 (3)	1 (1)	
Nephrogenic	4 (1)	3 (2)	1 (1)	
Pulmonary	11 (3)	10 (6)	1 (1)	
Neurological	52 (15)	20 (12)	32 (17)	
Cardiovascular	39 (11)	26 (16)	13 (7)	
Water and electrolytes	5 (1)	2 (1)	3 (2)	
Infectious	58 (16)	29 (17)	29 (15)	
Fall[5]	36 (10)	0 (0)	36 (19)	
Wound/ contusion	22 (6)	11 (7)	11 (6)	
Other[6]	45 (13)	30 (18)	15 (8)	
Communication problem, n(%)	101 (29)	27 (16)	74 (40)	0.000
Missing	((1))			
Amount of medication, mean (SD)	7.0 (3.9)	7.4 (3.8)	6.6 (3.9)	0.05
Missing	((7))			
Psychoactive medication, n(%)	84 (24)	36 (22)	48 (26)	0.403
Missing	((9))			

[1]One patient had triage colour red, orange and red were collapsed
[2]Care institution = nursing home or assisted living facility
[3]Cognitive disorder = dementia or mild cognitive impairment
[4]Charlson comorbidity index = indicates more and/or more severe comorbidities
[5]Admission diagnosis 'fall' = fall without other diagnosis. Note: The other diagnosis can still be associated with a fall
[6]Admission diagnosis 'other' = for example epistaxis, hypoglycaemia, arthritis

Figure 1. *Specification of atypical presentation of illness*



Atypicial presentation, n = 188 (53%)
Atypical presentation with known cause of geriatric syndrome, n = 125 (66%)
Atypical presentation with unknown cause of geriatric syndrome, n = 61 (32%)
None of the usual symptoms for the underlying disease, n = 29 (15%)

to a care institution (p = 0.000), and to have a higher delirium observation score (p < 0.001) (*table 2*).
The overall mortality rate one year after hospital admission was 31%. There was no significant difference in one-year survival for the type of illness presentation (p = 0.056) (*table 2*). If we excluded the fit elderly patients who had a fall by deselecting patients with a fall merged with a Charlson comorbidity index of 0 and 1, the group with atypical presentations was significantly associated with a lower one-year survival (27% versus 42%, p = 0.009).

DISCUSSION

This is one of the few studies to report on the prevalence of atypical illness presentations in elderly patients in the emergency department. The prevalence data indicate that a great proportion of patients aged 80 and older have an atypical illness presentation. Apart from Limpawattana et al., who found that approximately one-third of older patients present with atypical illness presentation, we found no other sources of prevalence data about atypical illness presentation in the emergency department for elderly patients, nor a univocal definition for atypical illness presentation. Much research has been done on geriatric syndromes or atypical illness presentation for single diseases. Furthermore, geriatric syndromes seem to be highly prevalent in the emergency department.[13,14] Lack of standardised terminology certainly indicates that proper research on this topic is difficult and an appropriate diagnostic approach and medical treatment is therefore difficult too. We know that physicians in the emergency department often lack geriatric training and are not confident in seeing elderly patients.[4] They are used to the classic medical model of diagnostic thinking, in which presenting symptoms and signs are aggregated into a diagnosis of a single pathological condition.[15] This approach does not sufficiently consider the complexity of older patients.[16] Therefore adequate training of emergency staff is essential.
Atypical disease presentation is more common in the frail elderly (59%) than in non-frail elderly (25%).[7] We perceived

Table 2. *Clinical outcome of elderly patients with and without atypical illness presentation*

Characteristics	All patients (n = 355)	Typical presentation (n = 167)	Atypical presentation (n = 188)	p-value
Admission duration ER (hours), mean (SD)	2.55 (1.4)	2.58 (1.6)	2.52 (1.2)	0.702
Duration hospitalisation (days), median(IQR)[1]	9 (4-15)	6 (2-12)	12 (5-17)	<0.01
Admission hospital, n (%)	233 (66)	111 (67)	122 (65)	0.755
Mortality in hospital, n (%)	23 (7)	11 (7)	12 (6)	0.938
Mortality at 1 year, n (%)	109 (31)	43 (26)	66 (35)	0.056
Discharge destination, care institution, n (%)	112 (32)	32 (19)	80 (43)	0.000
New discharge destination, care institution, n (%)[2]	54 (19)	14 (10)	40 (29)	0.000
New pressure ulcer, n (%)[1]	45 (20)	16 (15)	29 (25)	0.089
Missing	((13))			
Highest delirium observation score, median (IQR)[1]	2 (0-5)	1 (0-2)	3 (1-7)	<0.01
Missing	((26))			

[1]Only includes hospitalised patients
[2]Excluded patients already living in a care institution

this in our study as well, as patients with atypical illness presentations appeared to be more vulnerable. They were older, more often resided in a care institution, experienced higher rates of cognitive disorders and had more problems with communication in the emergency department. In emergency departments, impaired higher functions related to dementia or delirium are present in 25% of patients aged over 75 years.[4,17] These conditions can decrease the accuracy of the diagnosis of the main symptoms and mask potentially serious diseases.

The low Charlson comorbidity score in the group with atypical illness presentation seems to be contradictive. There are a couple of reasons for this: the Charlson comorbidity score[18] was not corrected for age and the underlying disease at time of admission was not included in the score. Furthermore, the group with an atypical illness presentation contains a considerable number of fit elderly patients with an isolated fall. This is likely because fit and active elderly patients have a higher probability of falling.

In nearly all cases an atypical illness presentation coincided with a geriatric syndrome, in which falling was the most frequently mentioned reason of admission. A previous study showed that 80% of the geriatric syndromes in the emergency department were caused by falls or confusion.[19] In our study falling accounted for 71% of patients with an atypical presentation. This is not surprising as falling is one of the main reasons for elderly patients to visit the emergency department (15-30%).

In our patients with atypical presentations, the most frequent diagnoses were fractures, and neurological and infectious diseases. In one-third the underlying disease of the atypical illness presentation was not determined. Unexplained falls accounted for the majority of undetermined atypical presentations. Elderly patients often cannot recall the fall because of syncope with memory loss or existing cognitive disorder.

Patients with an atypical illness presentation seem to have a worse clinical outcome.[3,4,9,11,14,17] We affirmed this in our study; they have a longer stay in hospital. However, we do not know whether atypical presentation is an independent risk factor. Possible causes for poor outcomes include comorbidity and frailty, a longer diagnostic process and missed diagnosis, less accurate or a delay in treatment,[20,21] illness severity, and more complications such as delirium. We found a high delirium observation score in this group, which must be interpreted cautiously because a high score can also be explained by the high degree of cognitive impairment in this group. Furthermore patients with atypical illness presentation are more often discharged to a care institution, which implies a decline in their health status.

The mortality rate one year after hospital admission was 31%. This is in line with a study from the Rooij et al. which showed a mortality rate of 35% after one year.[14] Although this study provides useful information on the prevalence of atypical illness presentations and the characteristics of these patients, we found no significant difference in one-year mortality. This is likely due to the high number of non-frail elderly who presented with an isolated fall without other complications. We found that if we excluded these patients, the group with atypical illness presentation is significantly associated with a lower one-year survival. However, the higher Charlson comorbidity index in this subgroup could be the reason for this association as well, as it implies more or more severe comorbidity.

A few important limitations need to be acknowledged. First, the retrospective nature of the study restricted data to those routinely collected. Important unmeasured factors include socioeconomic status, social support, education level, delay before admission and substance abuse. Furthermore the reporting rate of geriatric conditions in emergency department summaries was low. A former study showed that older patients present with an average of six geriatric conditions,[14] and often acquire new syndromes during hospital admission.[13] The underreporting of geriatric conditions actually reflects the under recognition of geriatric conditions during a hospital stay.[3,14] Second, potential recording bias may exist on retrospective analysis of medical records. However the study sought to minimise recording bias by incorporating the mutual review of the manner of presentation by two independent observers. Thirdly, this study focused on patients' leading symptom, which may underestimate the true prevalence of atypical presentation of other co-existing diseases, as we did not include the absence of physical signs at examination in our definition of atypical presentation. Fourth, co-existence of different components of atypical illness presentation (e.g. fall and delirium), was considered a single entity, which may overlook the cumulative effect of all elements of atypical illness presentation. Fifth, because this hospital is the only hospital in Amsterdam with an acute geriatric ward, patients with atypical illness presentation may preferably be referred to this hospital by general physicians. This may lead to an overestimation of the prevalence of atypical presentation.

In conclusion, atypical illness presentation, mainly falls, account for more than half of the elderly patients in the emergency department and this group seems to be vulnerable to adverse outcome. In 15% of these patients typical symptoms of an underlying disease are absent in the (hetero) anamnesis. Emergency department staff should be trained to recognise this group of patients to ensure proper clinical monitoring and timely treatment. Since atypical illness presentation is the result of multifactorial health conditions that occur when impairments in multiple systems accumulate,

the diagnostic workup for this group of patients should be a thorough diagnostic approach, such as a geriatric assessment.[22]

Finally, more research should be devoted to atypical illness presentation in the elderly patients by prospective multicentre survey.

DISCLOSURES

All authors declare that they have no conflict of interest. No financial support was received for the conduct of this study or preparation of this manuscript.

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CASE REPORT

Pitfall of modern genetics: recurrent erysipelas masquerading as autoinflammatory disease

E.J.W. Spierings, J.W.M. van der Meer, A. Simon*

Department of Internal Medicine, Radboud University Medical Centre, Nijmegen, the Netherlands,
*corresponding author: tel.: +31 (0)24-3618819, fax: +31 (0)24-3635126,
email: anna.simon@radboudumc.nl

ABSTRACT

A patient presented with recurrent episodes of fever and skin rash for eight years. DNA analysis of the NLRP3 gene revealed a mutation associated with autoinflammatory disease. After an initial positive response to the biological anakinra, the patient deteriorated. Reassessment revealed recurrent erysipelas. In conclusion, sometimes erysipelas-like skin rash is real erysipelas, and DNA results are not always the final answer.

KEYWORDS

Autoinflammatory, erysipelas, fever, genetic sequencing, misdiagnosis

What was known on this topic?
Autoinflammatory syndromes are often not easy to diagnose, but nowadays gene sequencing may provide a definite diagnosis more easily in many of these patients.

What does this add?
A new kind of diagnostic pitfall arises. As is demonstrated by the case report below, not every genetic variant that is found causes disease and the clinician may be led astray.

INTRODUCTION

Patients with recurrent fevers with or without a skin rash pose a difficult diagnostic problem.[1] Erysipelas, due to an infection with beta-haemolytic streptococci, is a very common cause of skin rash with fever. Occasionally *Staphylococcus aureus* and *Campylobacter jejuni* may cause erysipelas.[2] The latter organism likely causes erysipelas in patients with immunoglobulin deficiency. As classical erysipelas is caused by the erythrogenic toxin of haemolytic streptococci and not directly by the bacterium, the diagnosis may be difficult, since the focus harbouring the bacteria may be minute and hidden. Erysipelas-like skin lesions with episodes of fever are a well-known manifestation of familial Mediterranean fever[3] and of other auto-inflammatory syndromes such as cryopyrin-associated periodic syndrome (CAPS) and mevalonate kinase deficiency (also known as hyper-IgD syndrome).[4] The auto-inflammatory syndromes (formerly called periodic fever syndromes) are often not easy to diagnose, but nowadays gene sequencing may provide a definite diagnosis more easily in many of these patients. However, because of advanced genetic arrays, a new kind of diagnostic pitfall arises. As is demonstrated by the case report below, not every genetic variant that is found causes disease and the clinician may be led astray.

CASE REPORT

A 35-year-old Dutch male physician was referred because of recurrent episodes of itching skin rash over the buttocks (*figure 1A*). This was accompanied by spiking fever (≥ 40 °C) for two days with general malaise, back pain and bilateral inguinal lymphadenopathy. Raised C-reactive protein and neutrophilia (8.04 x 10^9/l) were present. The attacks had occurred 3-4 times/year for the last eight years, and seemed to be provoked by stress, but no other triggers were evident. Additional blood tests revealed negative ANA, normal complement and IgG levels, no gammopathy, elevated antistreptolysin O titre (800 IU/ml) and negative anti-DNAse B. Biopsy of subcutaneous fat and skin demonstrated superficial neutrophilic dermatitis, without bacteria. Family history revealed psoriasis in his father.

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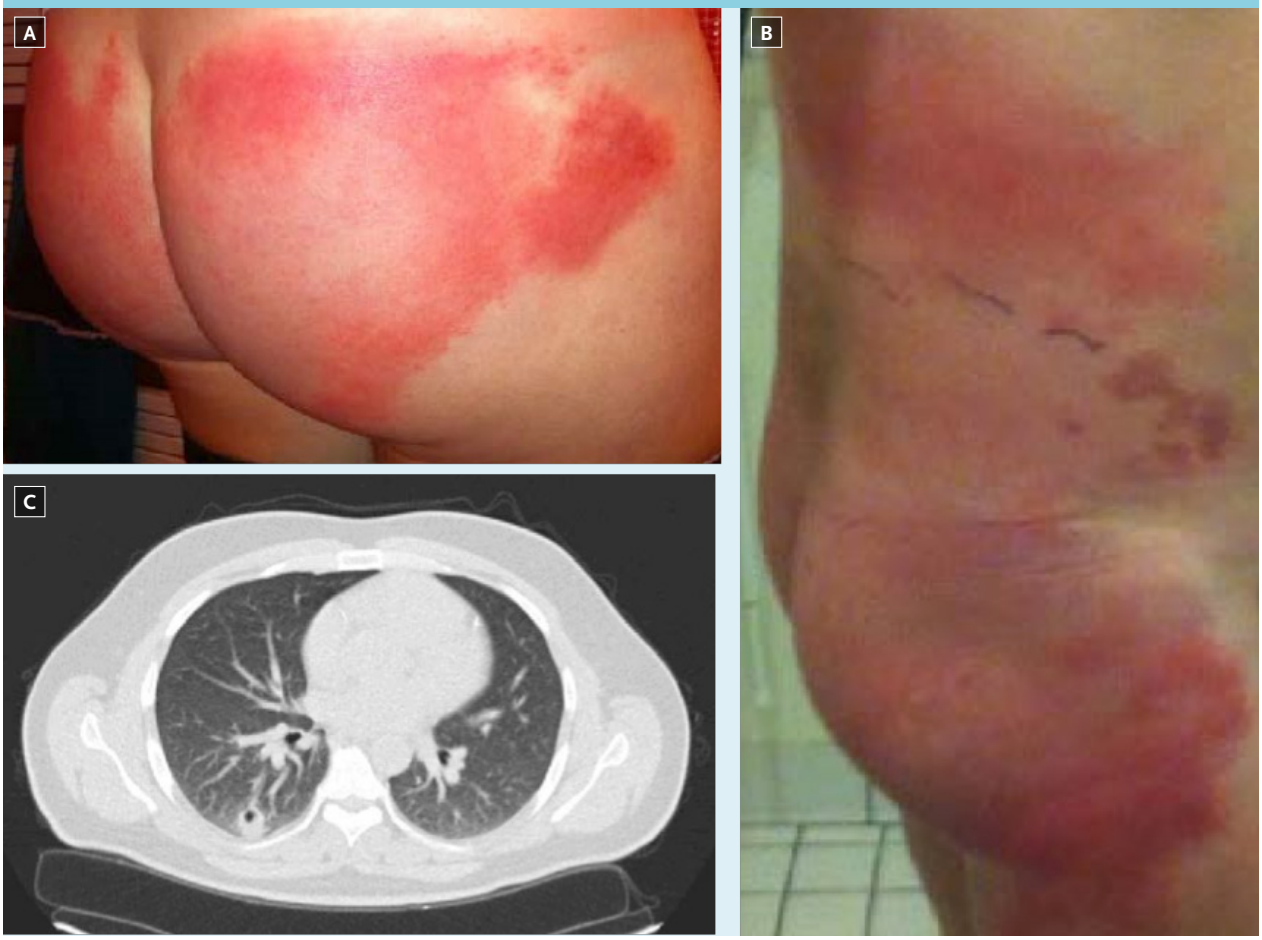
Our differential diagnosis included autoinflammatory disorders, and DNA analysis revealed a missense mutation in the NLRP3 gene (Leu677Pro). Mutations in the NLRP3 gene are linked with CAPS. This particular mutation was not previously known, therefore genetic analysis of his parents was requested. Meanwhile, he was started on treatment with the recombinant interleukin 1 receptor antagonist anakinra. This seemed effective as it shortened the episodes of fever. However, after several months an episode occurred with high fever (40.2 °C) and severe skin rash that did not respond to anakinra (*figure 1B*). A high dose of corticosteroids was added to the anakinra. This induced some improvement of the skin lesions, but a few days later the patient developed dyspnoea, thoracic pain and fever. A chest CT angiogram showed pleural fluid, pericardial fluid, lymphadenopathy and pulmonary infiltration (*figure 1C*). Analysis of pleural fluid demonstrated a chylous effusion, which was negative on Gram staining and on acid fast staining, and the cultures remained sterile. Bone marrow biopsy, immunophenotyping of peripheral blood and gastroduodenoscopy were performed (after cessation of treatment), which were all normal. A PET-CT scan demonstrated enhanced uptake of fluorinated desoxyglucose in a lesion in the right kidney and a cavitating intrapulmonary lesion. Serum *Aspergillus* antigen was negative. Upon cessation of treatment to enable the additional investigations, the patient improved rapidly, and all symptoms disappeared.

Reassessment of the medical history raised the suspicion of recurrent erysipelas of the buttocks, just as one of us had described 20 years earlier.[5] Culture of the perineum yielded group C haemolytic streptococci. The patient received eradication treatment with 10 days of clindamycin (600 mg three times a day). In the three years following, no new episodes of fever or skin lesions occurred. The DNA results from the patient's parents showed the same mutation in his father, who did not have similar symptoms.

DISCUSSION

Our final diagnosis in the patient reported here is recurrent erysipelas, possibly caused by group C haemolytic streptococci, with deterioration following immunosuppressive treatment. He had had these recurrent episodes of fever and skin rash for eight years, which

Figure 1. *A. Skin rash on the buttocks during fever episode. B. Deterioration of skin rash during a later episode while on anakinra and prednisone. C. Cavitating intrapulmonary lesion on chest CT scan*



always resolved spontaneously without antibiotic treatment. This is not common but has been described before.[5] Cessation of the immunosuppressive treatment (anakinra and corticosteroids) resulted in resolution of the symptoms, probably because of recovery of his immune system.

The results of the genetic array seemed to confirm our initial suspicion of an autoinflammatory disease, as did the initial positive response to anakinra. Probably, the anakinra only mitigated the systemic symptoms of the erysipelas episodes. This case demonstrates the need to remain critical, even when a definite mutation in a known disease-related gene is found. There is a growing number of case reports in the literature, in which claims are made for new genetic diseases, based on sequencing, where the diagnosis can be questioned. In the case of the hereditary autoinflammatory disorders, we recommend checking the detected genetic variants in the online INFEVERS database,[6] a registry of all the known hereditary autoinflammatory disorder mutations. Genetic analysis of family members can be indicated.

In conclusion, we describe a case of recurrent erysipelas that was misdiagnosed as an autoinflammatory disorder based on genetic results. This demonstrates that 1) sometimes, erysipelas-like skin rash is real erysipelas, and 2) even in case of a genetic variant in a known disease gene, clinicians need to stay alert for the possibility of a misdiagnosis.

DISCLOSURES

All authors declare no conflict of interest. No funding or financial support was received.

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CASE REPORT

A fatal case of metastatic squamous cell carcinoma in a patient with myositis ossificans traumatica

I.N. Vlasveld[1]*, H. Scheper[1], J. Stalenhoef[1], J.M. Baas[2], J. van Dissel[1,3]

Departments of [1]Infectious Diseases, [2]Oncology, Leiden University Medical Centre, Leiden, the Netherlands, [3]RIVM Centre for Infectious Disease Control, Bilthoven, the Netherlands
*corresponding author: tel.: +31 (0)71-5262613, fax: 071-5266758, email: I.N.Vlasveld@lumc.nl

ABSTRACT

Myositis ossificans traumatica is a rare disease associated with chronic wounds and fistulae. Chronic ulcers, fistulae and wounds can transform into squamous cell carcinoma, the so-called Marjolin's ulcer. We describe a rapid, progressive and fulminant course of a metastatic squamous cell carcinoma arising from a chronic wound in a patient with myositis ossificans traumatica.

KEYWORDS

Marjolin's ulcer, myositis ossificans traumatica, squamous cell carcinoma

INTRODUCTION

Myositis ossificans traumatica is a rare condition characterised by heterotopic bone formation of soft tissues. Based on clinical and histological data, the condition is often misdiagnosed as an infection or malignancy.[1] However, a few cases of myositis ossificans traumatica transforming into a malignant tumour have been published.[2,3] Ossifications by myositis ossificans traumatica may lead to cutaneous perforation accompanied by low-grade chronic infection with ulceration and sinus tracts. Chronic ulcers and wounds are known risk factors for the development of a type of squamous cell carcinoma called Marjolin's ulcer.[4] We describe a patient with myositis ossificans traumatica and a rapidly progressive and fatal course of metastatic squamous cell carcinoma primarily originating from a chronic ulcerated wound.

CASE REPORT

The patient, a 62-year-old woman, was admitted with general malaise, pain and swelling of the right leg. She had a known history of myositis ossificans traumatica since 1984 when she developed bilateral ossifications of the thighs, after removal of a lipoma from the right quadriceps region. Subsequently, she developed a chronic wound with multiple fistula on the right thigh which developed into a chronic and polymicrobial infection of the ossified muscles.[5] Surgical debridement was not considered feasible as this would inevitably result in amputation of the right leg. With suppressive antibiotic therapy the infection remained controlled and she maintained functionality of her leg. Over the years, flares of infection were treated with antibiotics, mainly beta-lactam antibiotics, depending on cultures and antibiotic susceptibility.

In the last two months she had been suffering from general malaise and developed increasing pain, ulceration and swelling of her right thigh. On clinical examination the patient appeared weak. Examination of the right leg revealed an extensive, ulcerating and smelly wound with a diameter of approximately 20 cm (*figure 1*). On the medial side a large granulating, easily bleeding tumour of approximately 8 cm was visible. Laboratory investigations revealed hypercalcaemia of 3.36 mmol/l (2.15 to 2.55 mmol/l) and an increased parathyroid hormone-related peptide of 2.5 pmol/l (< 0.7 pmol/l). An ultrasound of the leg excluded deep vein thrombosis. A biopsy of the ulcerating tumour was performed and showed squamous cell carcinoma. A CT-thorax revealed multiple pulmonary nodules and two cavitating lesions in the left lower lobe and right upper lobe (*figure 2*).

A biopsy of one of the lung lesions was not conclusive. Cultures of the lung lesions were negative. An additional

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Figure 1. *Panel A shows the patient's leg four years ago; Panel B shows a very extensive and ulcerating wound of approximately 20 cm with a granulating tumour of 8 cm on the medial side*

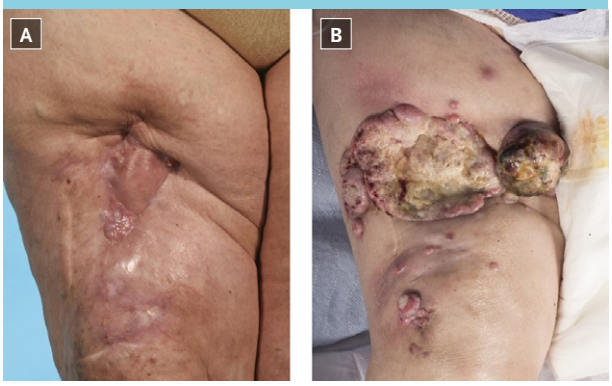


Figure 2. *CT-thorax of the patient shows a pulmonary nodule in the left lower lobe and a cavitary lung lesion in the right lower lobe*

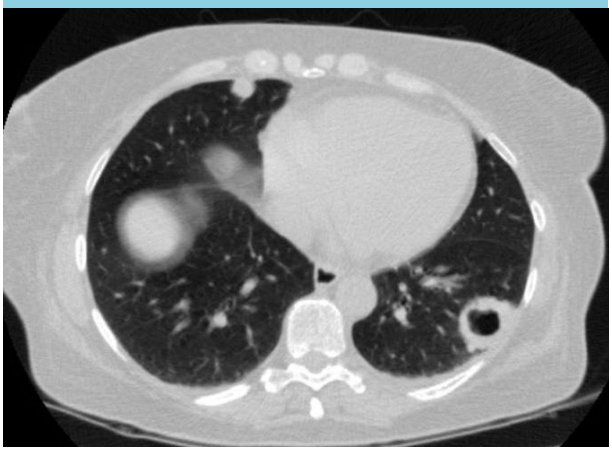
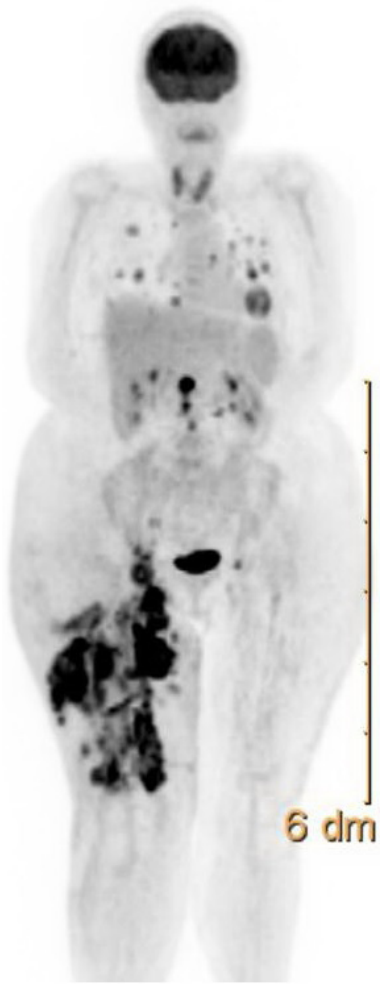


Figure 3. *PET-CT shows greatly enhanced metabolism of the right thigh, inguinal lymph nodes, para-aortic lymph nodes and lung lesions*



PET-CT showed enhanced metabolism of the right thigh, inguinal lymph nodes, para-aortic lymph nodes and bilateral, cavitating lung lesions (*figure 3*). Biopsies of inguinal lymph nodes were positive for metastatic squamous cell carcinoma. Additional immunohistological staining on biopsies of the right thigh and the inguinal lymph nodes showed the same p53 mutant pattern. Based on the long-lasting ulcerating wound, the locoregional metastatic pattern and the proven p53 mutations in both biopsies, we concluded that the metastatic squamous cell carcinoma most likely originated from the ulcerating tumour in her thigh. The patient was treated with bisphosphonates for her hypercalcaemia and started cetuximab for local control of the squamous cell carcinoma. Because of her clinical deterioration, palliative care was started and the patient was discharged to a hospice, where she passed away shortly after discharge.

DISCUSSION

Myositis ossificans is characterised by heterotopic bone formation in soft tissues. Differentiating myositis ossificans from a soft tissue malignancy can be challenging and is based on clinical and pathological characteristics. Due to aggressive growth and pathological characteristics such as atypia and mitotic activity, myositis ossificans is sometimes misdiagnosed as malignancy, particularly osteosarcoma.[1,6] Myositis ossificans can transform into osteosarcoma.[2,3] Myositis ossificans can be divided into a progressive and a traumatic type. Progressive myositis ossificans (or Munchmeyer's disease) is a congenital disease with autosomal dominant inheritance. Symptoms arise in early childhood; different muscles, tendons and ligaments may be affected. Traumatic myositis ossificans involves single muscles, muscle groups

subjected to prior surgery or trauma and other soft tissues. Thigh and arm muscles are mostly affected, but also the hand, intercostal and jaw muscles can be affected.[6-8] The exact mechanism for the pathogenesis of myositis ossificans traumatica is not clear. It has been suggested that trauma and intramuscular haemorrhage induce proliferation of vascular granulation tissue resulting in metaplasia to cartilaginous bone.[8] Trauma induces a signal of bone morphogenetic protein, resulting in proliferation of mesenchymal cells to osteoblasts or chrondroblasts.[9] Surgical treatment of the ossifications and affected muscles may be considered, but since repeated trauma can lead to new ossification this should be avoided as far as possible.

Chronic ulcers, fistulas and wounds can transform into squamous cell carcinoma. Marjolin's ulcer was first described in 1828 by Jean Nicholas Marjolin. In 1903 Da Costa reported malignant transformation of these ulcers.[4] The incidence is low and represents about 2 to 5% of all squamous cell carcinomas of the skin.[10] Transformation of a chronic wound or ulcer into a malignancy tends to be slow and develops over 20-35 years.[11] Marjolin's ulcers can be present anywhere on the skin but the trunk and extremities are particularly affected. The aetiology of the malignant transformation is not completely understood. It has been hypothesised that chronic wounds increase the likelihood of mutations. Due to fibrosis and avital tissue, circulating lymphocytes cannot reach and destroy the mutated cells resulting in impaired immunological activity.[11] Marjolin's ulcers have a high risk of recurrence and metastasising compared with other types of squamous cell carcinoma. Determining the primary site of metastatic squamous cell carcinoma by immunohistochemistry is generally not possible.[12] The three-year survival for lymphogenic metastatic Marjolin's ulcer is 35-50%.[13] Patients with burn scars, chronic inflammatory dermatoses, ulcers, osteomyelitis and fistulas have an increased risk of transformation into squamous cell carcinoma.[14] Physicians should be alert that patients with chronic wounds who develop increasing size, pain or bleeding tendency of the wound might have a malignant transformation and a biopsy might be warranted to exclude this potentially devastating condition.

CONCLUSION

To the best of our knowledge, we present for the first time a case of a rapid, progressive and fulminant course of metastatic squamous cell carcinoma arising from a chronic wound in a patient with myositis ossificans traumatica. Differentiating myositis ossificans from malignancy is challenging. In case of enlargement, pain, or bleeding tendency in patients with chronic fistulae, wounds and ulcers a histological biopsy should be considered.

DISCLOSURES

All authors declare no conflict of interest. No funding or financial support was received.

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CASE REPORT

A new mutation in the calcium-sensing receptor gene causing hypocalcaemia: case report of a father and two sons

M.K. Schoutteten[1]*, B. Bravenboer[2], S. Seneca[3], K. Stouffs[3], B. Velkeniers[2]

[1]Department of Internal Medicine, Maastricht University Medical Centre, the Netherlands, [2]Department of Endocrinology, University Hospital Brussels, Belgium, [3]Centre for Medical Genetics, University Hospital Brussels, Research Unit Genetics and Fertility, Vrije Universiteit Brussel, Brussel, Belgium, *corresponding author: tel.: +31 (0)43-3875007, fax: +31 (0)43-3875006, email: melanie.schoutteten@hotmail.com

ABSTRACT

Background: Regulation of calcium is mediated by parathyroid hormone (PTH) and 1.25-dihydroxyvitamine D3. The calcium-sensing receptor (CaSR) regulates PTH release by a negative feedback system. Gain-of-function mutations in the *CaSR* gene reset the calcium-PTH axis, leading to hypocalcaemia.

Patients and methods: We analysed a family with hypocalcaemia. The proband was a 47-year-old man (index, patient I_1), who presented with paraesthesias in both limbs. He has two sons (patient II_1 and II_2). The probands' lab results showed: serum calcium of 1.95 mmol/l, albumin 41 g/l, phosphate 0.81 mmol/l and PTH 6.6 ng/l (normal 15-65 ng/l). Based on this analysis, we suspected a hereditary form of hypocalcaemia and performed genetic testing by polymerase chain reaction and Sanger sequencing of the coding regions and intron boundaries of the *CaSR* gene. Genetic analysis revealed a new heterozygous mutation: c.2195A>G, p.(Asn732Ser) in exon 7. The lab results of patient II1 showed: serum calcium of 1.93 mmol/l, phosphate 1.31 mmol/l, albumin 41 g/l, and PTH 24.3 ng/l. His genotype revealed the same activating mutation and, like his father, he also lost his scalp hair at an early adolescent age. Patient II_2 is asymptomatic, and has neither biochemical abnormalities, nor the familial *CaSR* gene mutation. He still has all his scalp hair.

Conclusions: 1) The c.2195A>G, p.(Asn732Ser) mutation in exon 7 of the *CaSR* gene leads to hypocalcaemia, and has not been reported before in the medical literature. 2) Possibly, this mutation is linked to premature baldness.

What was known on this topic?
Autosomal dominant hypocalcaemia is a syndrome causing hypocalcaemia by activating the calcium-sensing receptor (CaSR). Several genes have been identified.

What does this add?
This publication adds the knowledge of a newly discovered activating mutation in the *CaSR* gene of a father and one son. Moreover, we report the remarkable presentation of alopecia in both patients.

KEYWORDS

Autosomal dominant hypocalcemia, calcium-sensing receptor, hypocalcemia

INTRODUCTION

Chronic hypocalcaemia is a frequent problem and can be life-threatening. Most patients report paraesthesia, but hypocalcaemia can also cause muscle cramps, seizures and cardiac arrhythmias. Long-term complications of chronic hypocalcaemia include tissue calcifications in the brain and kidneys, cataract and osteoporosis. Parathyroid hormone (PTH) is responsible for minute-to-minute regulation of the plasma calcium.[1,2] Hence, causes of hypocalcaemia are classified according to PTH concentration *(table 1)*.

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Table 1. *Functional classification of hypocalcaemia*

PTH absent
Hereditary hypoparathyroidism Acquired hypoparathyroidism (surgical or radiation induced) Hypomagnesaemia
PTH ineffective
Chronic renal failure Vitamin D deficiency (inadequate diet or sunlight, defective vitamin D metabolism due to medication, malabsorption) Pseudohypoparathyroidism
PTH overwhelmed
Severe, acute hyperphosphatemia (tumour lysis, acute renal failure, rhabdomyolysis) Osteitis fibrosa after parathyroidectomy

The parathyroid cells express calcium-sensing receptor (CaSR), a G-protein-coupled receptor providing a negative feedback system to the calcium-PTH axis.[3-5] CaSR is mainly located in parathyroid glands and the renal tubule. By sensing ionised calcium, the CaSR regulates PTH release and PTH-independent calciuresis. Gain-of-function mutations in the *CaSR* gene shift the calcium-PTH axis to a lower set point. The mutant CaSR becomes activated by a low ionised serum calcium concentration and subsequently inhibits PTH release. Autosomal dominant hypocalcaemia (ADH) is a syndrome characterised by an inappropriately low PTH according to a symptomatic hypocalcaemia and a relative hypercalciuria.[1,4,5] A small subgroup of ADH patients develop additional renal loss of sodium, chloride and magnesium, resulting in hyperreninaemia, hyperaldosteronism, hypokalaemia and metabolic alkalosis. Most of them present during childhood, which is diagnosed as Bartter's syndrome type 5.[4,6]

We present a family of a father and his sons diagnosed with ADH caused by a new mutation in the *CaSR* gene.

CASE REPORT

A 47-year-old bald man (index, patient I_1) was seen with complaints of paraesthesia in both limbs. No Chvostek sign could be provoked. His past medical history included autoimmune hypothyroidism. Blood analysis showed a serum calcium of 1.95 mmol/l at presentation. His phosphate was 0.81 mmol/l and PTH was low 6.6 ng/l *(table 2)*. The calciuresis was high at 7.6 mmol/24 h. Patient I_1 was initially diagnosed with idiopathic hypoparathyroidism and treated with calcitriol. We performed genetic testing by polymerase chain reaction (PCR) and Sanger sequencing of the coding regions and intron boundaries of the *CaSR* gene. Genetic analysis by PCR amplification and DNA sequencing revealed a new mutation in the gene coding for CaSR: c.2195A>G, p.(Asn732Ser) in exon 7. Since patient I_1 is a heterozygous carrier, genetic counselling was recommended with his two sons.

One son (patient II_1) was analysed at the age of 25. He reported a tingling sensation in both hands. He smoked 25 cigarettes a day. Physical examination revealed no Chvostek sign, hypertension 140/70 mmHg, and a remarkable baldness. PCR of the *CaSR* gene exposed the same mutation as patient I_1 had. Lab results of patient II_1 showed hypocalcaemia 1.92 mmol/l with a normal concentration of albumin, phosphate and PTH. Calciuresis was also high-normal at 6.3 mmol/24 h *(table 2)*.

Table 2. *Biochemical analysis of blood and urine at presentation*

	Reference	Patient I_1	Patient II_2	Patient II_3
Calcium mmol/l	2.1-2.55	1.95	1.93	2.19
Albumin g/l	32.0-47.0	41	41	40
Phosphate mmol/l	0.90-1.50	0.81	1.39	1.07
Magnesium mmol/l	0.70-1.00	0.53	0.82	/
Intact PTH ng/l	1.3-6.8	6.6	24.3	33.7
25-hydroxy vitamin D nmol/l	> 90	/	98	34.4
1.25-Dihydrox vitamin D pmol/l	50-110	60	/	/
TSH mIU/l	0.4-6.2	2.360	1.160	1.130
24 h urine collection		**Patient I_1**	**Patient II_2**	**Patient II_3**
Volume ml		1950	2800	/
Calcium mmol/l		3.92	2.25	/

PTH = parathyroid hormone; TSH = thyroid stimulating hormone.

The youngest son (patient II_2) is asymptomatic and still has all his scalp hair. No mutation in the calcium-sensing receptor could be found.

DISCUSSION

Activating mutations of the *CaSR* gene can cause symptomatic hypocalcaemia. ADH has a wide clinical spectrum.[5,7] As in our cases, most patients report paraesthesia in the limbs, but chronic severe hypocalcaemia might be life-threatening.[1,4,5,7] The phenotype is determined by the calcium level. Signe et al. found that the severity of clinical neurological symptoms is inversely related to serum calcium levels.[7]

The *CaSR* gene is located on chromosome 3q13.5,8. The first activating mutation was described by Pollak et al. in 1994.[9] The CaSR mutation database (http://www.casrdb.mcgill.ca) contains more than 40 known activating mutations in *CaSR* gene.[5] Also several recent case reports have demonstrated new activating mutations.[8,10] Genetic analysis in patient I_1 and patient II_1 revealed another new activating mutation: c.2195A>G, p.(Asn732Ser) in exon 7. Because this mutation has not been described before, it is classified as 'variant of uncertain significance'. In silico analysis of the mutation shows that substitution of asparagine by serine is most probably pathogenic. Most ADH patients are heterozygous. One family is known with a homozygote mutation, but this is not associated with a more severe phenotype.[5]

Remarkably, our affected patients are completely bald. Alopecia is a known symptom occurring in polyglandular autoimmune syndrome type I (PGA I).[1,5] Although patient I_1 has an autoimmune hypothyroidism, no Addison's disease, mucocutaneous candidiasis, keratopathy, vitiligo, parietal cell atrophy, insulin-dependent diabetes mellitus or autoimmune hepatitis is known in this family. Therefore, it is unlikely that the alopecia in our patients fits into an autoimmune syndrome. Moreover, PGA I is inherited as an autosomal recessive trait and has a childhood onset.[1,5] Another hereditary syndrome is an autosomal recessive mutation in the *hairless* gene located on chromosome 8p12.[11]

However, neither a biopsy, nor genetic counselling towards the *hairless* gene was performed. Most probably, a mutant gene coding for alopecia is located close to the *CaSR* gene and was simultaneously inherited.

Treatment of hypocalcaemia is symptomatic. Hypocalcaemia is treated by calcium supplementation. Calcitriol or alphacalcidol is added to stimulate intestinal calcium absorption. Normalisation of hypocalcaemia can cause a rise in hypercalciuria resulting in kidney stone formation. Therefore, treatment with active vitamin D and calcium supplementation should be performed carefully to prevent symptoms and arrhythmias, but also to prevent possible long-term complications of this treatment. Each patient requires regular monitoring of serum calcium, calciuria and renal function. Adding hydrochlorothiazide can limit calciuria.[4]

Ideally, the activated CaSR should been blocked to provide a more pathophysiological therapy. Calcilytic drugs are being studied to block the CaSR and thus provide a more pathophysiological approach in treating these patients. This could be a very promising novel therapeutic approach for ADH.[12]

In conclusion, we present a father and his son who were diagnosed with ADH. Their activating mutation in the *CaSR* gene leads to symptomatic hypocalcaemia. In both family members a new mutation in the CaSR was found. Possibly, a polymorphism of a gene related to alopecia is located near the *CaSR* gene and is also dominantly inherited.

DISCLOSURES

The authors declare no conflicts of interest.

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PHOTO QUIZ

A young woman with acute renal failure

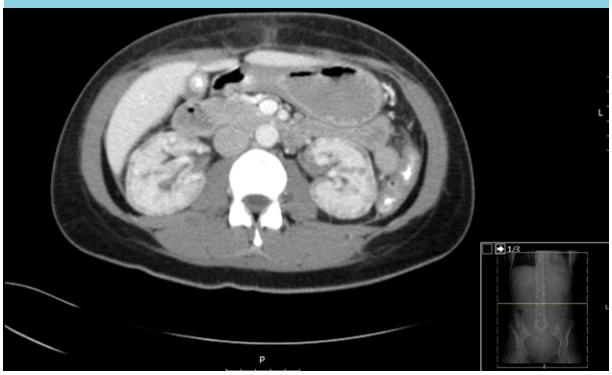
R.F. Crane

Intensive Care Center, University Medical Center, Utrecht, the Netherlands, tel.: +31 (0)88-7571140, fax: +31 (0)88-7561160, email: r.f.crane@umcutrecht.nl

CASE REPORT

A 32-year-old woman was admitted after placental abruption with foetal demise at 33 weeks of pregnancy. Her medical history included two caesarean sections. She developed extensive bleeding and diffuse intravasal coagulation and was admitted to the intensive care unit for resuscitation. Due to uncontrollable bleeding, she underwent emergency laparotomy, which showed a uterine rupture. After suturing the rupture, the patient stabilised. However, in the hours following surgery, she developed oligo-anuria despite an adequate circulation. Due to persistent anuria, haemodialysis was started. Urine analysis was unremarkable. Contrast-enhanced computed tomography was performed.

Figure 1. *Contrast-enhanced computed tomography showing bilateral hypo-intense renal cortices*



WHAT IS YOUR DIAGNOSIS?

See page 257 for the answer to this photo quiz.

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ANSWER TO PHOTO QUIZ (PAGE 256)

A YOUNG WOMAN WITH ACUTE RENAL FAILURE

DIAGNOSIS

Based on the clinical history of hypovolaemic shock as an obstetric complication and the characteristic findings of a hypo-intense renal cortex on computed tomography, a diagnosis of renal cortical necrosis (RCN) was made. RCN is a rare cause of acute kidney injury (AKI) in developed countries, characterised by oligo-anuria with typical computed tomography findings of a hypo-intense renal cortex in the early stages and cortical calcifications in later stages.[1] Traditionally, RCN is associated with obstetric complications such as (pre-)eclampsia, uterine haemorrhage and puerperal sepsis. Rarer causes include sepsis, hypercoagulability and major surgery.[2,3]

Although the exact pathogenesis remains incompletely understood, a number of factors causing impaired renal cortical perfusion contribute to the development of RCN, notably arterial vasospasm, arterial thrombosis, endothelial damage and circulatory shock. Several physiological and pathophysiological changes in pregnancy explain the association between RCN and obstetric complications: the increased susceptibility of the arterial circulation to vasopressors, the hypercoagulable state and the possibility of endothelial damage due to pre-eclampsia, HELLP syndrome or exposure to foetal material during delivery or abortion.[3]

In a clinical setting of arterial vasoconstriction combined with endothelial damage, the renal cortex is particularly vulnerable as the renal vasculature is especially sensitive to endothelin, a potent endothelium-derived vasopressor, thus exacerbating arterial vasospasm when there is concomitant endothelial damage. The renal medulla, which operates at low tissue oxygen levels in normal physiology, can more easily switch to oxygen-independent metabolism, which explains why the ischaemia only affects the cortex.

The incidence of RCN decreases with improving maternal care, accounting for less than 2% of AKI in Europe, compared with 7% in developing nations.[3,4] However, as computed tomography and renal biopsy are not routinely performed in critically ill patients with AKI, RCN may be under-diagnosed. The diagnosis should be considered especially in obstetric patients, where 20% of AKI is due to RCN. Therapy for RCN is supportive. The prognosis is poor compared with many other causes of AKI, with less than one-third of patients partially recovering renal function.[3] This partial recovery may be explained by sparing of the juxtamedullary glomeruli. After being dependent on haemodialysis for 36 days, our patient's renal function gradually recovered to an estimated glomerular filtration rate of 26 ml/min.

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PHOTO QUIZ

Cutaneous adverse effects of immunotherapy

M. Slingerland[1]*, M.F. Benner[2], P.M. Jansen[3], R. van Doorn[2]

Departments of [1]Medical Oncology, [2]Dermatology, [3]Pathology, Leiden University Medical Center, Leiden, the Netherlands, *corresponding author: tel.: +31 (0)71-5263464, email: m.slingerland@lumc.nl

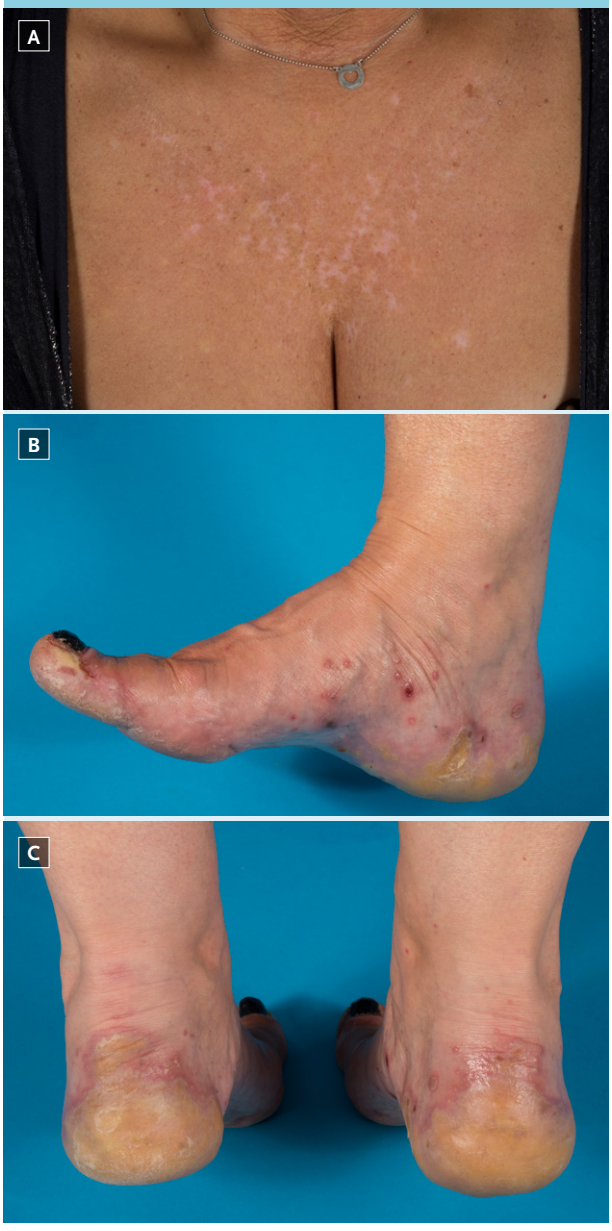
CASE REPORT

A 51-year-old fit woman visited the oncology department because of metastasised (right femur, liver and breast) melanoma for which she was treated with nivolumab, an antibody that targets the programmed cell death 1 (PD-1) receptor on T cells. After the 13th treatment cycle the patient developed sharply demarcated, irregularly shaped depigmentation on the chest *(figure 1A)*. Evaluation of the computed tomography (CT) scan before the 17th cycle only showed a residual lesion in the right femur, which means there was an almost complete immune-related response based on the immune-related response criteria.[1] Shortly after the 17th cycle she developed discrete, slightly scaly, erythematous papules distributed over the extremities, in particular on the palms and dorsomedial aspect of the feet (*figure 1B*). The plantar surface and the heels showed hyperkeratosis with a violaceous margin (*figure 1C*). In addition, whitish reticulate striae on the buccal mucosa were noted. The eosinophil count in the blood was not raised. The patient had not used any other medications.

WHAT IS YOUR DIAGNOSIS?

See page 259 for the answer to this photo quiz.

Figure 1. *A) Depigmentation on the chest. B,C) Erythematosquamous papules and plaques on the feet*



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ANSWER TO PHOTO QUIZ (PAGE 258)

CUTANEOUS ADVERSE EFFECTS OF IMMUNOTHERAPY

DIAGNOSIS

Histopathological examination of skin biopsies taken from squamous papules located on the flank and on the hand both revealed a lichenoid interface dermatitis with vacuolar degeneration of the epidermis and presence of Civatte bodies (*figure 2*). We made a diagnosis of lichenoid mucocutaneous eruption and vitiligo due to the use of nivolumab. These cutaneous adverse events reflect T-cell mediated immunity towards keratinocytes and melanocytes, activated by immune checkpoint inhibition. In the development of vitiligo due to immunotherapy specific T-cells against MART-1, gp100 and tyrosinase seem to play a role. But also MART-1 reactive antibody responses are suggested to be important. The mechanisms of breaking tolerance to MART-1, which lead to antibody responses, may be dependent on T-cell help, but deserve further investigation.[2] More than 15% of patients treated with anti-PD1 antibodies experience cutaneous adverse effects.[3] In 82 patients treated with nivolumab at an institution in Australia, 17% of patients developed a lichenoid eruption and 17% developed vitiligo.[4]

Development of vitiligo or skin eruption in patients receiving anti-PD1 antibody therapy for melanoma is associated with better survival.[5] In patients treated with ipilimumab or adoptive T-cell transfer the occurrence of vitiligo has been reported, but not of lichenoid skin eruption. Treatment with topical and systemic corticosteroids resulted in significant improvement. The patient's melanoma has already been in remission for 17 months.

Figure 2. *Histopathology of plantar skin lesion showing lichenoid interface dermatitis (magnification 100x)*

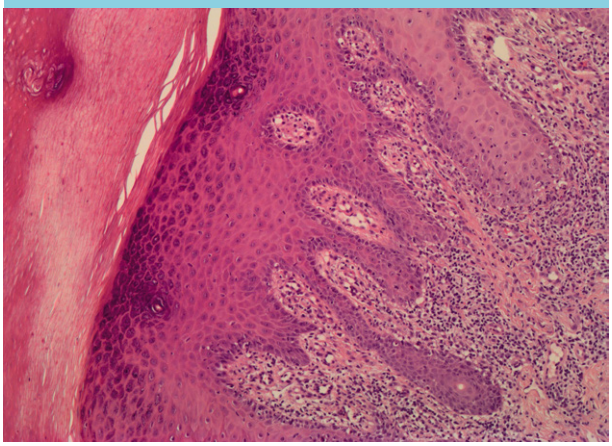

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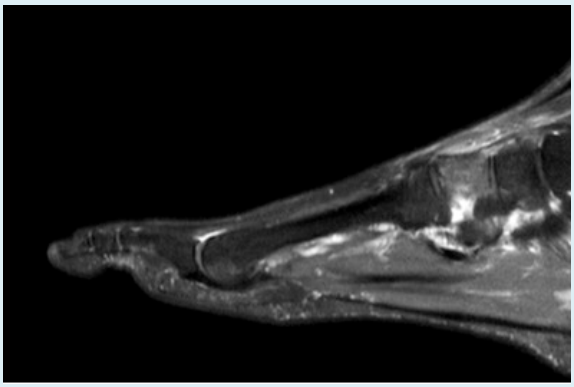
PHOTO QUIZ

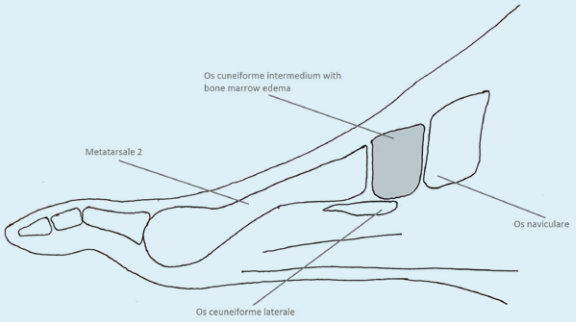
Invalidating painful foot

E.M.V.J. Donders*, H.J. Voerman

Department of Internal Medicine, Amstelland Hospital, Amstelveen, the Netherlands,
*corresponding author: tel. +31 (0)6-53970565, fax: +31 (0)20-5125109, email: emvjdonders@gmail.com

Figure 1. *Sagittal view of left foot in proton density weighted SPectral Attenuated Inversion Recovery (SPAIR), showing bone marrow oedema in the intermediate cuneiform bone*





CASE REPORT

A 62-year-old otherwise healthy nurse visited the outpatient clinic because of a five-month history of a sudden onset of pain in her left foot without preliminary trauma. She describes a painful, sleeping sensation in this foot when walking. Therefore she is unable to fulfil her job. Prior treatment with diclofenac and physical therapy have had no effect. During four weeks of immobilisation in plaster she had no symptoms, but since she is up and using the leg again she is suffering from an unrelenting VAS pain score of 5. On physical examination, the left ankle is slightly swollen, reddish in colour and warm. There is tarsometatarsal tenderness without palpable abnormalities, and no sensory or motor deficits. Laboratory tests including uric acid show no abnormalities. Additional MRI shows bone marrow oedema in the intermediate cuneiform bone, with no other abnormalities (*figure 1*). The bone scan shows in three-phase positive deviation in the left foot root, at the area of the cuneiform bone (*figure 2*). The pictures are shown with the patient's permission.

WHAT IS YOUR DIAGNOSIS?

See page 261 for the answer to this photo quiz.

Figure 2. *Focal uptake in cuneiform bone*

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ANSWER TO PHOTO QUIZ (PAGE 260)
INVALIDATING PAINFUL FOOT

DIAGNOSIS

Based on the symptoms and the results of MRI and bone scan this fits best with transient osteoporosis of the intermediate cuneiform bone, also known as bone marrow oedema syndrome.

Transient osteoporosis is an uncommon syndrome of unknown aetiology, characterised by self-limiting pain and obvious focal osteopenia and oedema on imaging, visible within eight weeks after the onset of the pain. The diagnosis is made by exclusion based on MRI and is often delayed because of the low prevalence and nonspecific signs.[1] It is best described in the hip among women in the last trimester of pregnancy and middle-aged men. Painful symptoms gradually subside and reach full recovery without intervention within 18 months.

Because transient osteoporosis resolves on its own, treatment focuses on minimising the symptoms and preventing any damage to the bones while they are weakened by the disorder. Our patient is being treated according to complex regional pain syndrome protocol,[2] with dimethyl sulfoxide cream which inhibits the impulse conduction in peripheral sensory nerves, in combination with acetylcysteine for combating free radicals that might be associated with the onset of complex regional pain syndrome on the basis of a sterile inflammation. Bone strength will return to normal.

CONCLUSION

Transient osteoporosis of the intermediate cuneiform bone with complex regional pain syndrome.

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