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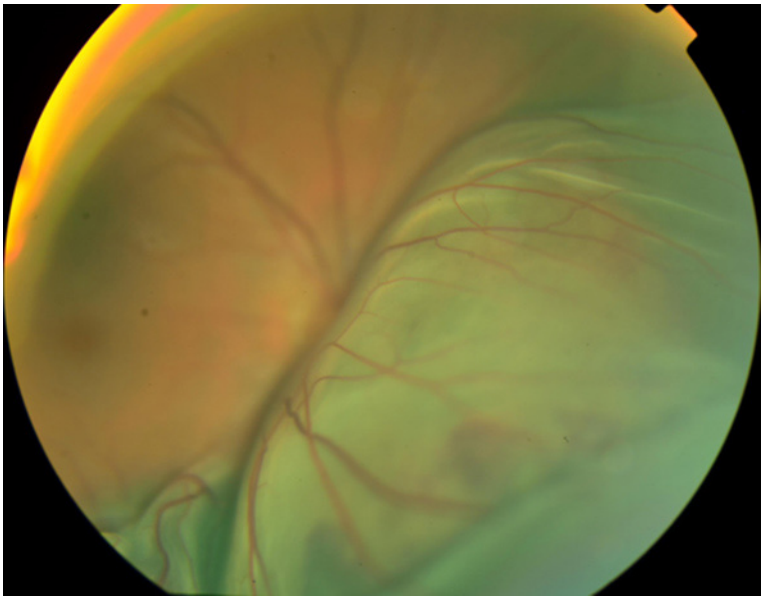

A young man with vision loss; what do you see?

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EDITORIAL

Treatment decisions in the elderly: tailor-made thinking

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The number of people of 65 years or older is growing rapidly. It is estimated that in Europe 17% of the European population is ≥ 65 years (total 88 million), increasing to 157 million people in 2060 (Eurostat Statistics). However, there is no such thing as 'the older patient'. There is an enormous heterogeneity present in our older patients, as compared with younger, generally more healthy patients. This is contributable to a number of factors.

The biological age of any patient depends largely on their medical history, actual comorbidity, medication use and physical capacity. In the elderly, besides the somatic axis, three more axes are used to describe the patient: psychiatric, functional and social status. In general, older people will have multimorbidity, polypharmacy, cognitive decline and decreased physical activity. Studies show that 55-98% of older patients have multimorbidity, i.e. two or more chronic diseases.[1] More often than not, these problems interfere with each other, making it harder for the clinician to treat each different, in itself simple, condition. With decreased life expectancy due to advanced age, quality of life and taking into account the 'cost and benefits' should play a bigger role in the decision-making process regarding (invasive) treatment options. The positive and negative effects for the patient should be carefully weighed, bearing in mind that most older patients will have an increased risk of complications, such as delirium and will need more time for rehabilitation.[2] That being said, there is a risk of undertreatment of older people if the only thing taken into account is age, with no regard for the status of this unique older patient. Treating an older patient with calendar age as the only criterion is likely to lead to overtreatment of the frail older patient and undertreatment of the biologically younger patient.

More evidence-based medicine (EBM) should be obtained to ensure optimal treatment decisions for our older patients. In their article, Mooijaart et al. explain which measures should be taken to improve EBM in older patients: systematic acknowledgement of the patient situation, generating more scientific evidence and increasing doctors' experience and expertise.[3]

Apart from the need for more EBM for our elderly patients, there is growing acknowledgement of the need for tools on decision-making in treatment options for biologically ageing patients. In their article, Van Loon et al. conducted a survey among Dutch nephrologists to assess the role of cognitive, functional and psychosocial issues regarding dialysis initiation.[4] These issues, and especially cognitive problems, are considered relevant; however, Van Loon et al. concluded that systematic assessment of the above-mentioned three issues is not in the standard care. Screening measurements are used, but it is yet to be determined what their value is with regards to improving decision-making.

We all want to identify those patients, in whom forgoing treatment is the better choice. However, generally doctors are more prone to act, and are reluctant to stop or not initiate treatment. A recently published report by the Royal Dutch Medical Association (KNMG) describes the motivations for clinicians to continue treatments, and the mechanisms installed in our care system that are sustaining this way of practising medicine.[5] It also provides medical professionals with measures to reach a level of appropriative care for our older patients.

As there is no standard older patient, there also is no standard way of treating that patient. In general, guidelines have little to offer for the multimorbid patient. With a patient using multiple medications and suffering from more than two chronic diseases, the clinician has to be able to weigh all the different aspects to reach the best plan of action for this particular patient with this particular combination of problems. In all branches of medicine, colleagues are searching for tools to identify the elderly patient, for whom forgoing treatment should at least be seriously considered.

One of the terms often used regarding this type of older patient is frailty. Frailty is a syndrome, describing a patient with three or more of the following criteria present: unintentional weight loss, self-reported exhaustion, weakness, slow walking speed and low physical activity.[6] However, frailty indexes alone do not seem to suffice in

the triage of patients eligible for invasive treatments such as chemotherapy or surgical procedures.

A factor that is not always taken into account is the opinion of the patient. In our experience, when given adequate information and ample time to think about and discuss the matter with loved-ones, older patients are very capable of making decisions concerning their future, even when it comes to starting, stopping or forgoing medical procedures or treatments. This will, however, require a different approach from the clinician, and a switch from a modus of foremost wanting to 'act' to a position in which not starting treatment is an equally possible outcome as starting one.

Of course, we should not make the patients' wishes the only factor in decision-making. For every suggested treatment or procedure, we as clinicians have the obligation to assess the benefits and risks for our patients. If, based on medical reasons, the risks outweigh the benefits, the decision should be made not to start the treatment or procedure. However, in most cases there remains some level of debate whether a treatment will be more beneficiary or detrimental to the patient. In those cases, frailty indexes or other screening instruments can help to ease the decision-making. Furthermore, in all of the cases in which there is debate about a treatment plan, the point of view of the patient should play an important role.

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REVIEW

Treatment of multicentric Castleman's disease in HIV-1 infected and uninfected patients: a systematic review

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ABSTRACT

Background: Multicentric Castleman's disease (MCD) is frequently associated with human-herpesvirus (HHV)-8, especially in human immunodeficiency virus (HIV)-1 co-infections. The optimal treatment is unclear. This systematic review provides an overview of available evidence on chemotherapeutic and monoclonal antibody therapies directed against CD20, interleukin (IL)6 or IL6 receptor.

Methods: A systematic literature search of Embase, Medline, Web-of-Science, Scopus, PubMed publisher, Cochrane and Google Scholar was conducted for trials and cohort studies on MCD therapy. Baseline characteristics and reported endpoints were summarised and treatment efficacy was assessed by overall mortality rates.

Results: 1817 studies were identified providing five trials and 14 cohort studies on 666 patients, including one randomised placebo-controlled trial. Ten studies reported on 450 HIV-1 positive patients. Most HIV-1 positive (99.7%), and 24.4% of HIV-1 negative patients were HHV-8 infected. Study populations and methods varied considerably. The use of rituximab was associated with better treatment responses and survival compared with chemotherapy without rituximab in HHV-8 associated, predominantly HIV-1 infected, MCD patients. Anti-IL6(receptor) antibodies might be promising second-line or salvage agents, at least in HIV-1 and HHV-8 negative patients. Kaposi sarcoma (re)activation with rituximab and MCD progression to aggressive lymphoma, or haemophagocytic lymphohistiocytosis were important complications.

Conclusions: Optimal MCD treatment for HIV-1 and/or HHV-8 positive or negative patients remains unclear. The available evidence is of low quality due to study designs, treatment allocation bias, and publication bias. MCD patients remain at risk for developing lymphomas or haemophagocytic lymphohistiocytosis. Rituximab may have survival benefits for HHV-8 associated MCD, but it is related to Kaposi sarcoma exacerbations.

KEYWORDS

Anti-CD20, anti-IL6, chemotherapy, HIV-1, human herpesvirus 8, multicentric Castleman's disease

INTRODUCTION

Multicentric Castleman's disease (MCD) is a lymphoproliferative disorder affecting B-lymphocytes and plasma cells. An infection with the human herpesvirus (HHV)-8, especially in human immunodeficiency virus (HIV)-1 infected patients, has been frequently associated with MCD development.[1,2] Three histological categories of MCD are identified: the plasma cell, hyaline vascular and mixed variants. The plasma cell variant is present in 80-90% of MCD cases. An HHV-8 infection results in the production of human and viral (HHV-8 DNA encoded) pro-inflammatory interleukin (IL)6 that induces plasma cell proliferation, and appears to be of importance in MCD pathogenesis.[3-5] MCD is diagnosed by histological evidence of affected tissues in patients with pro-inflammatory clinical symptoms.

Despite the ever-increasing number of patients with adequately controlled HIV-1 by combination antiretroviral therapy (cART), MCD incidence in HIV-1 patients is increasing.[6] The incidence in HIV-1 patients has been estimated at 2.3 per 10,000 patient-years in the pre-cART era prior to 1996, and 8.3 per 10,000 patient-years since 2000. In the general population, ten-year MCD

prevalence is approximately 2.4 per million persons.[6,7] The clinical course of MCD is seldom self-limiting and, if left untreated, associated with high mortality rates. However, the optimal treatment for MCD remains unclear.[8] MCD treatment strategies include chemotherapy, anti-CD20 antibodies (rituximab) and the use of antibodies directed against IL6 or the IL6 receptor (anti-IL6(R)). This systematic review aims to summarise available evidence of these MCD therapies and their potential complications.

METHODS

The primary purpose of this systematic review was to provide an overview of all conducted trials, prospective and retrospective cohort studies on chemotherapeutic or immunomodulatory (anti-CD20 and anti-IL6(R)) treatments of HHV8-associated and HHV8-unrelated MCD, both in HIV-positive and HIV-negative patients. The study conduct was in accordance with the PRISMA statement for systematic reviews.[9]

Search strategy

Studies were extracted from an extended search in Embase, Medline (OvidSP), Web-of-Science, Scopus, PubMed publisher, Cochrane Library and Google Scholar up to 16 December 2014. Results were limited to retrospective or prospective cohorts and clinical trials in humans from the English literature. The search was not restricted by age, HIV-1 status, or HHV-8 status. We searched the following medical subject heading terms in titles and abstracts: "Castleman" OR "Angiofollicular lymph node hyperplasia" AND "Chemotherapy" OR "Anti-CD20" OR "Rituximab" OR "Anti-IL6" OR "Tocilizumab" OR "Siltuximab". Duplicate findings were identified and removed. Initial screening of the titles and abstracts excluded animal studies, guidelines, identical publications and identified studies primarily on MCD. The titles and abstracts of the remaining studies were assessed on eligibility. We excluded studies that did not primarily report outcomes on the clinical effectiveness of chemotherapy, anti-CD20 or anti-IL6(R) for MCD, provided insufficient data on therapy outcomes or were available as conference abstracts only. We assessed the full text of studies on eligibility if the title and abstract were inconclusive. All eligible trials and cohort studies had to report on at least ten MCD patients on identical treatment consisting of chemotherapeutic, anti-CD20 or anti-IL6(R) therapies. Only studies with data on treatment outcomes and survival outcomes were included for the analysis. Case reports were excluded. We identified reports on identical patient series and included the most recent records. The final selected studies for analysis were cross-referenced for potential omitted relevant studies.

Data extraction

The following information was extracted from the studies: principle author, year of publication, study design, number of patients included, patient characteristics (age, gender), HIV-1 infection, HHV-8 status, cART, tissue histology, clinical course, therapy received, and treatment outcomes. The number of deaths and median or mean follow-up time were evaluated in all studies. If available, the reported survival rates were extracted for comparability reasons unless no survival rates were reported and the authors provided an alternative efficacy endpoint. We evaluated incidences of Kaposi sarcoma, lymphoma, and haemophagocytic lymphohistiocytosis (HLH) if reported. The results were reviewed on (pooled) descriptive characteristics and therapy outcomes. The levels of evidence and recommendations were graded according to the Oxford Centre for Evidence-Based Medicine levels of evidence.[10] No interferential statistics were computed due to the heterogeneity of study designs and lack of uniform study endpoints.

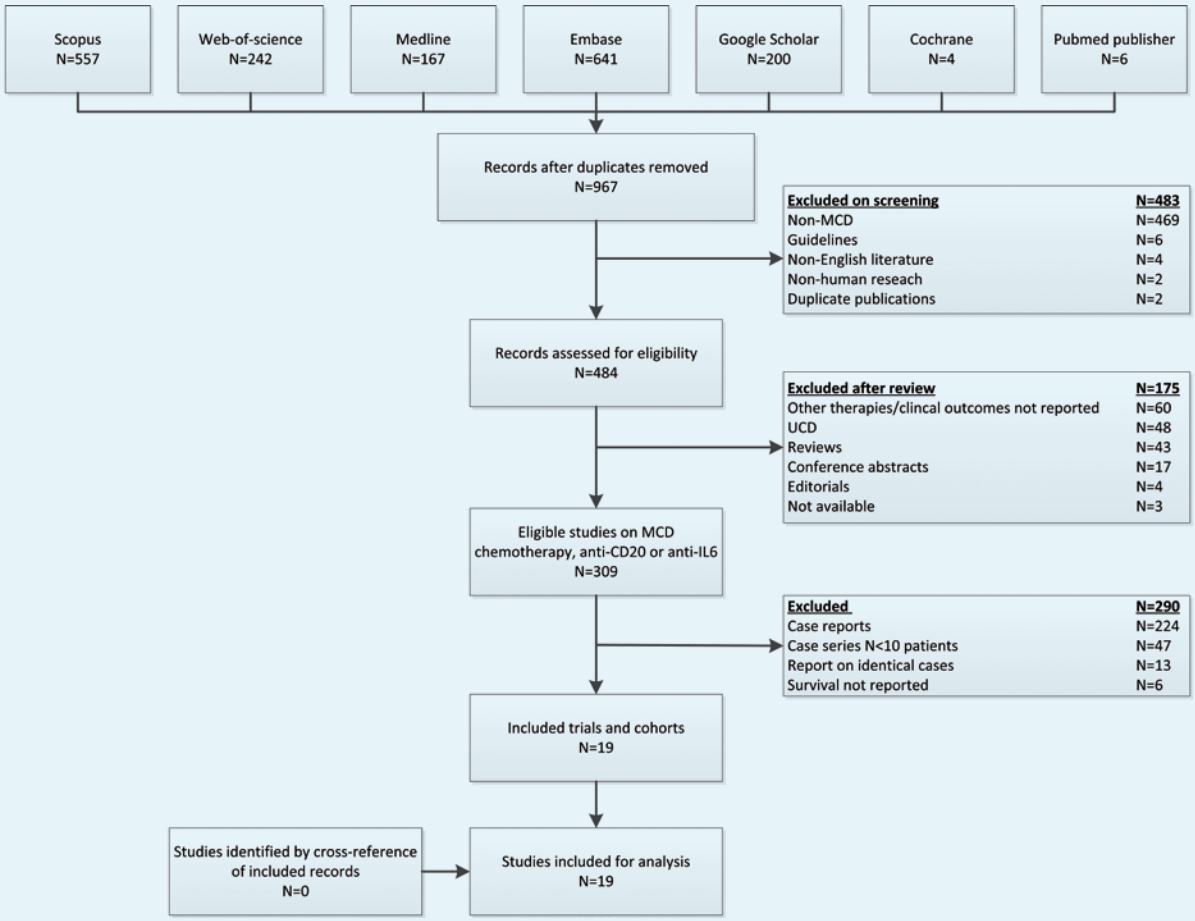
RESULTS

Study and patient characteristics

Of 1817 studies identified by the search, 309 were eligible studies on MCD chemotherapy, anti-CD20 or anti-IL6(R) (*figure 1*). These included 224 case reports, 47 case series on less than ten patients, and 13 reports on identical patient series. Nineteen studies, including five trials and 14 cohort studies, were included for analysis and provided data on 666 predominantly male (79.9%) patients with MCD. The level of evidence of all trials was grade 2B because of limited follow-up or absence of control groups. One cohort was grade 2B due to size, reported outcomes, follow-up duration and identification and correction of potential confounders.[11] All other cohorts were low-quality studies of grade 4. Median age was 43 (range: 37-65) years. Data on gender and age were not available in one study.[12] HIV-1 was excluded by serology in all patients in five studies,[13-17] and in 13 of 21 patients in one study.[18] One trial did not report HIV-1 status.[19] Available HIV-1 test results were positive in 100% of patients in the remaining 11 studies, except in one retrospective cohort study (64% HIV-1 positive).[20] In total, 450 patients were HIV-1 positive and 216 were either HIV-1 negative or had an unknown HIV status. Apart from one study,[21] all studies were from the cART era and reported cART coverage in these studies was 65.4% (270/430 patients) at MCD diagnosis. The reported HIV-1 RNA suppression rate < 500 copies/ml was 40.8% and median CD4 cell count was 221 (range: 148-398) cells/mm^3.

MCD diagnosis was established by histological tissue examination in 98.5% of patients. Results on MCD variants were reported in 64 HIV-1 positive patients,[20-23] and 192 HIV-1 negative patients.[13,14,16-19] Only the plasma cell

Figure 1. *Search strategy and article selection.*



IL = interleukin; MCD = multicentric Castleman's disease; UCD = unicentric Castleman's disease

and mixed variants were observed in 54.7% and 45.3% of HIV-1 patients respectively. MCD variants in HIV-1 negative patients were 49.5% plasma cell, 25.5% hyaline vascular, and 25.0% mixed variants. Splenectomies were performed in 39 patients and 29/39 were reported in studies conducted prior to 2008. Kaposi sarcoma foci were reported in four studies and apparent in 17 of 91 (18.7%) histologically examined MCD tissues.[21,22,24,25] No histopathological evidence for lymphoma was found at MCD diagnosis although 13 studies either did not report results or excluded patients with evidence of lymphoma. The reported HHV-8 detection methods varied. Two studies did not report on HHV-8 status,[16,26] two studies omitted the description of the detection methods,[19,20] and six studies described multiple HHV-8 detection methods.[11,12,15,22-24] Quantitative HHV-8 polymerase chain reaction (PCR) in plasma was used in 11 studies,[11,15,17,18,22-25,27-29] including one trial that excluded HHV-8 infected patients.[17] ELISA or immunofluorescence antibody assays to latent nuclear antigens were used in three studies,[13,22,24] and six studies used HHV-8 PCR or immunohistochemistry on biopsy tissues.[11,12,15,21,23,24] Excluding the studies that did not report or include HHV-8 patients,[16,17,26] HHV-8 test results were available for 416/525 patients (79.2%) and HHV-8 was demonstrated in 83.4% (347/416) of patients. These patients included 99.7% (326/327) of HIV-1 positive patients compared with 24.4% of HIV-1 negative patients with HHV-8.

MCD therapy and outcome

MCD treatments, survival and main therapy outcomes are shown in *table* 1. Results are categorised according to HIV-1 status. Six cohort studies were predominantly on chemotherapy alone,[12,14,16,21,22,29] nine studies were either on rituximab alone,[23,24] or on rituximab/chemotherapy combined,[11,15,20,25-28] and four studies, including the only randomised placebo-controlled double-blind clinical trial on MCD therapy, were on anti-IL6(R).[13,17-19] The cumulative number of patients treated by chemotherapy was 212, by rituximab this was 241 (including 163 patients on rituximab alone), and 130 were treated by anti-IL6(R). Eighty-three patients were treated by other or unreported therapies or received palliative care only. Of 212 patients on chemotherapy, 107 were treated by

Table 1. *Treatment outcomes reported in studies on MCD patients*

Reference	Study Design (n)	Primary therapy (n)	HIV+ (%)[a]	HHV8+ (%)[a]	Death (%)	FU (mo.)	Reported efficacy endpoint	Endpoint achieved (%)	Comments
HIV-1 status positive									
1996 Oksenhendler	Retrospective cohort (n = 20)	Chemotherapy (16)[b] Other (4)	100	100	68.8 75.0	10	-	-	-
2002 Oksenhendler	Retrospective cohort (n = 60)	Chemotherapy (60)	100	100	20.0	20	-	-	All patients received vinblastine or etoposide.
2004 Loi	Retrospective cohort (n = 11)	Chemotherapy (11)	100	100	45.5	22	-	-	All patients received cyclophosphamide, chlorambucil or anthracyclines with steroids at unspecified disease stages
2005 Guilhot	Retrospective cohort (n = 12)	Chemotherapy (11)[c] Rituximab (1)	100	100	36.4 100	41	-	-	-
2007 Bower	Non-randomised open-label single-arm phase II trial (n = 21)	Rituximab (21)	100	100	4.8	12	Year 2 overall survival rate	95.0	Treatment naive and patients with histological evidence of microlymphoma excluded
2007 Gérard	Non-randomised open-label single-arm phase II trial (n = 24)	Rituximab (24)	100	100	8.3	12	Year 1 overall survival rate	92.0	Second-line rituximab after MCD control by chemotherapy. Lymphoma and KS were excluded
2011 Bower	Prospective cohort (n = 61)	Rituximab (35) Rituximab +/ etoposide (14) Other/NR (12)	100	100	8.2 - 33.3	50	Year 2 overall survival rate	94.0 - 42.0	Mortality and overall survival rate calculated on rituximab and rituximab+/ etoposide treated patients. Patients on etoposide had poorer performance state
2011 Hoffmann	Retrospective cohort (n = 52)	Rituximab (10) Rituximab +/ chemotherapy (4)[d] Chemotherapy (22)[d] Other/NR (14/2)	100	NR	10.0 - 45.5 50.0	27	Year 1 complete response	94.0 - 39.0 14.0	Mortality and complete response rate calculated on rituximab and rituximab+/chemotherapy patients
2011 Stebbing	Retrospective cohort (n = 52)	Rituximab (28) Rituximab +/ etoposide (14) Other (10)	100	100	36.5 - -	49	Year 2 overall relapse-free survival	89.0 - -	Mortality and overall relapse-free survival rate calculated on whole cohort. Seven patients with early progressive disease not in survival analysis

Table 1. *Treatment outcomes reported in studies on MCD patients*

Reference	Study Design (n)	Primary therapy (n)	HIV+ (%)[a]	HHV8+ (%)[a]	Death (%)	FU (mo.)	Reported efficacy endpoint	Endpoint achieved (%)	Comments
2012 Gérard	Retrospective cohort (n = 113)	Rituximab (44) Rituximab +/ chemotherapy (4)[e] Chemotherapy (65)[e]	100	100	16.7 - 43.1	50	Year 2 overall survival rate	93.2 - 67.9	Mortality and overall survival rate calculated on rituximab and rituximab+/ chemotherapy treated patients. Cytostatic monotherapy prior to rituximab in all patients
2012 Ramasamy	Retrospective cohort (n = 11)	Rituximab +/ thalidomide (11)	64.0	91.0	9.1	22	-	-	Three patients had response after second round of rituximab+/ thalidomide
2014 Uldrick	Prospective cohort (n = 17)	Rituximab + liposomal doxorubicin (17)	100	100	17.6	58	Clinical complete response after 2 cycles	88.0	Fourteen patients were pretreated by chemotherapy, rituximab, or antivirals. Consolidation therapy in 15 patients
HIV-1 status negative or unknown									
2005 Nishimoto	Non-randomised open-label single-arm phase II trial (n = 28)	Tocilizumab (28)	0	7.1	3.6	15	Week 16 any MCD disease improvement	100	Treatment naive and experienced patients
2012 Xu	Retrospective cohort (n = 19)	Rituximab +/ chemotherapy (1)[f] Chemotherapy (12)[f] Other/none (6)	0	0	0 25.0 16.7	32	-	-	All patients had MCD with renal involvement
2013 Dossier	Retrospective cohort (n = 18)	Rituximab +/ etoposide (10) Rituximab +/ chemotherapy (3)[g] Chemotherapy (5)[g]	0	100	0 0 60.0	18	-	-	Four patients were lost to FU. 2/3 deaths were due to PEL
2013 Kurzrock	Non-randomised open-label single-arm phase I trial (n = 37)	Siltuximab (37)	NR	2.7	8.1	29	Day 36 clinical benefit response≥1 component	87.0	Treatment naive and experienced patients
2013 Zhu	Retrospective cohort (n = 10)	Chemotherapy (10)[h]	0	NR	20.0	34	-	-	-
2014 Kawabata	Retrospective cohort (n = 21)	Tocilizumab (n = 12) Other (n = 9)	0	0	8.3 22.2	98	-	-	Tocilizumab used in patients with severe or refractory MCD

Table 1. *Treatment outcomes reported in studies on MCD patients*

Reference	Study Design (n)	Primary therapy (n)	HIV+ (%)[a]	HHV8+ (%)[a]	Death (%)	FU (mo.)	Reported efficacy endpoint	Endpoint achieved (%)	Comments
2014 van Rhee	Randomised double-blind placebo-controlled trial (n = 79)	Siltuximab (53) Placebo (26)	0	0	3.8 15.4	14	Week 18 durable tumour symptomatic response	34.0 0	Treatment naive and experienced patients. Randomization according to baseline steroid use. All patients received best supportive care

[a] Percentage positive results of patients tested. [b] Vinblastine (9), cyclophosphamide (3), adriamycin/bleomycin/vinblastine (4). [c] Etoposide (4) +/methylprednisolone (1), vinblastine (3) +/methylprednisolone (1), cyclophosphamide/methylprednisolone (1) +/vinblastine (1). [d] Doxorubicin (4) +/vinblastine (2) +/rituximab (1), etoposide (4) +/doxorubicin/bleomycin (3) +/vincristine (1), cyclophosphamide/hydroxydaunorubicin/vincristine/prednisone (3) +/etoposide (1) +/antivirals (4) +/rituximab (3). [e] Chemotherapeutics not specified. [f] Cyclophosphamide/vincristine/prednisone (6) +/thalidomide (2) +/hydroxydaunorubicin/rituximab (1), cyclophosphamide/corticosteroid (2), vincristine/prednisone (2). [g] Vinblastine/etoposide/bleomycin (3), cyclophosphamide/hydroxydaunorubicin/vincristine/prednisone (1) +/etoposide (1) +/rituximab (1), cyclophosphamide/rituximab (1) +/doxorubicin/etoposide/prednisone (1). [h] Cyclophosphamide/vincristine/prednisone (4), cyclophosphamide/hydroxydaunorubicin/vincristine/prednisone (6).
FU = follow-up; HIV =human immunodeficiency virus; HHV-8 = human herpesvirus type-8; KS = Kaposi sarcoma; MCD = multicentric Castleman's disease; mo. = months; NR = not reported; PEL = primary effusion lymphoma.

single cytostatics to control MCD recurrences including vinblastine, cyclophosphamide, chlorambucil, etoposide, doxorubicin and vincristine. Combination chemotherapy was used in 40 patients as first- or second-line regimens. One study did not specify the chemotherapies used in 65 patients.[11] Excluding prior corticosteroid exposure, rituximab was used as first-line therapy in 151 patients as single agent (n = 95) or in combination with chemotherapy (n = 56), predominantly etoposide (n = 36). As second-line therapy, rituximab monotherapy was used in 68 patients and rituximab/chemotherapy (predominantly liposomal doxorubicin) combined in 22 patients with (chemo)therapy dependent MCD. The majority of patients (105/130, 80.8%) on anti-IL6(R) therapy received prior systemic therapies.
The overall all-cause mortality rate was 137/666 patients (20.6%) at a median follow-up of 27 months. Mortality rates were 25.3% in HIV/HHV-8 positive and 10.6% in HIV-1 (and for the large majority HHV-8) negative patients. The causes of death were progressive MCD in 17.5% and 34.8% of HIV-1 positive patients and HIV-1 negative patients, respectively, infections (or AIDS in HIV-1 positive patients) in 12.3% and 13.0%, multi-organ failure in 4.4% and 4.5%, progression to lymphoma in 39.5% and 8.7%, and unreported or unknown in 21.9% and 39.0%. Kaposi sarcoma was the cause of death in 5/114 (4.4%) HIV-1/HHV-8 positive patients only. The mortality rates according to treatment modalities received during reported follow-up were 36.8% for chemotherapy alone, 10.1% for rituximab with or without chemotherapy, 7.7% for anti-IL6(R) and 30.1% for other therapies. Of note, one cohort study did not specify deaths according to therapy modalities and could not be used.[28] Furthermore, another cohort study only reported on deaths of MCD patients that developed non-Hodgkin's lymphoma.[12]

Ten studies defined endpoints that showed broad variety in definitions. Overall, first- or second-line rituximab containing therapy was more able to sustain remission and increase survival than chemotherapy alone, at least in HHV-8 positive, and often HIV-1 positive, MCD patients. The reported proportions of patients who achieved the endpoints were at least 88.0% when rituximab was part of the treatment, and at the most 67.9% with chemotherapy alone. For anti-IL6(R) monotherapy, the majority of patients achieved improvement on at least one disease component although durable tumour and symptomatic responses remained around 40% in this highly pre-treated group of predominantly HIV-1 and HHV-8 negative MCD patients.

Kaposi sarcoma, HLH and lymphoma

Kaposi sarcoma, HLH and lymphoma were frequently diagnosed prior to MCD diagnosis or during follow-up. Excluding the three antiIL6(R) trials and four studies that did not report on Kaposi sarcoma,[14,16,18,28] Kaposi sarcoma was apparent in 244 of 429 patients. Progression of Kaposi sarcoma during follow-up occurred in 55 (12.8%), predominantly HIV-1 positive (96.4%), MCD patients. The majority of Kaposi progressions (67.3%) were observed in studies of patients treated with rituximab. In the studies that specifically reported on lymphoma development during MCD follow-up (n = 416), the incidence was 15.1%. Three studies reported on HLH, which was diagnosed in 34.3% of 143 patients at MCD diagnosis or during follow-up.[11,15,22]

DISCUSSION

The current systematic review indicates that the use of rituximab appears to provide a survival benefit, both

in HIV-1 positive and HIV-1 negative, HHV-8 associated MCD patients in first- or second-line therapy (Grade B recommendation). Anti-IL6(R) showed promising results in controlling disease activity, at least in HIV-1 and HHV-8 negative patients (Grade B recommendation).

The optimal treatment of HHV-8 positive and HHV-8 negative MCD patients remains unclear and largely based on low-quality evidence. Etoposide and liposomal doxorubicin have been used with favourable results in combination with rituximab in HHV-8 associated MCD (Grade C recommendation). The use of chemotherapy alone was generally associated with higher mortality rates than in combinations with rituximab. This indicates that it might be preferable not to use chemotherapy without rituximab (Grade C recommendation). Despite treatment, the clinical course of MCD is frequently complicated by exacerbations of Kaposi sarcomas, lymphoma development, or HLH, and the mortality remains high.

Disease progression to (often HHV-8 related) lymphoma is frequently observed in MCD and appears to be partially prevented by including rituximab in MCD treatment. In MCD, HHV-8 infected B-lymphocytes are able to coalesce and form microscopic lymphoma, which may express the CD20 antigen.[5,30,31] Ongoing IL6 receptor activation might be involved in the lymphoproliferative differentiation of these B-cells. Rituximab's protective effect could be due to the resulting HHV-8 infected B-lymphocyte depletion, which decreases cytokine levels involved in further B-cell proliferation. Despite the effect of rituximab on lymphoma development, HLH and Kaposi sarcoma are prevalent concomitant clinical complications in MCD. Kaposi sarcoma seems to be related to the rituximab exposure, and almost exclusively in HIV-1 infected patients. HIV-1 and HHV-8 can both trigger HLH, which is associated with a high mortality rate.[32] The combination HHV-8 infection and IL6 overproduction in MCD could result in a dysfunctional cascade of cytokine overproduction with T-lymphocyte and macrophage activation causing HLH, especially in immunocompromised HIV-1 patients.[33-36] Furthermore, a possible relation has been observed between low B-lymphocyte counts and increased risk for Kaposi sarcoma development with increased expression of HHV-8 gene products in Kaposi sarcomas after rituximab therapy.[37-39] A marked decrease in Kaposi sarcoma flares was observed if rituximab was combined with single-agent chemotherapies, mainly etoposide. The clinical implications of these observations are unclear. In our opinion, HHV-8 positive MCD patients should be evaluated for clinical signs of Kaposi sarcoma or its presence in tissue biopsy prior to the initiation of rituximab. If Kaposi sarcomas are present, the concomitant administration of chemotherapeutics (etoposide, liposomal doxorubicin or paclitaxel) might be recommended. However, the possible benefit of adding chemotherapeutics to rituximab on Kaposi flares or survival needs to be further evaluated. Furthermore, the effects of HHV-8 suppression by antiviral agents on Kaposi sarcoma and HLH development in the context of rituximab therapy for MCD is yet unknown. Last, the usefulness of cytokine levels and HHV-8 viral load for the monitoring of treatment effect, disease activity or for predicting patients at risk for MCD relapse after clinical remission and development of subsequent lymphoma, Kaposi sarcoma or HLH warrants further evaluation.[40,41]

The monoclonal antibodies against IL6 and the IL6 receptor, siltuximab and tocilizumab, are not yet approved for the European market for the treatment of MCD. Siltuximab has a favourable opinion based on the benefit-to-risk balance and European market approval is recommended.[42] Tocilizumab has only been approved for the treatment of rheumatoid arthritis. Evidence is available from trials on the subgroup of MCD patients without HIV-1 or HHV-8 and the efficacy of these drugs in other patient groups remains to be elucidated. Issues on drug safety especially for the orphan medicine siltuximab are another important issue because of the limited experience with this drug. Additional trials on tocilizumab and siltuximab in MCD are ongoing.[43,44]

The overall level of evidence of the studies was low and no definite conclusions can be drawn on the available evidence. All studies were obviously biased in several ways. Important confounders as HHV-8 status, HIV-1 infections, Karnofsky performance scores, detailed treatment information and the presence of Kaposi sarcoma or microlymphomas in tissue examinations were not uniformly investigated or reported. Unmeasured confounders have likely occurred during the covered time period, which make comparisons difficult. The large number of case reports and case series indicate publication bias, which cannot be evaluated due to the absence of registration databases for these studies. Selection bias of patients is a major limitation for interpreting the studies. The results of the cohort studies are predominantly influenced by possible treatment-allocation bias; the patients at highest risk for death received palliative care only or had aggressive and often fatal lymphomas for which chemotherapy was warranted. Therefore, the results should be interpreted cautiously. Lastly, an in-depth evaluation of treatment responses according to HHV-8 status might have been the preferred method from a pathophysiological point of view. The large amount of missing data regarding HHV-8 status, the heterogeneous use of variable HHV-8 detection methods, and other study limitations hindered this separation.

CONCLUSION

Based on the results of the present systematic review we cannot provide conclusive evidence-based treatment recommendations for optimal MCD therapy in HIV-1 infected or uninfected patients. Although the available evidence is of low quality, the use of rituximab appears to

provide a survival benefit in HHV-8 associated MCD, and anti-IL6(R) therapy might offer a treatment option after first-line treatment failure for HIV-1 negative patients without HHV-8 associated MCD.

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APPENDIX

Search terms used in the medical databases for the literature search in the systematic review on the treatment of multicentric Castleman's disease.

Embase.com

('angiofollicular lymph node hyperplasia'/de OR (((angiofollicul* OR angiolymphoid* OR angiomat* OR 'Giant Lymph') NEAR/3 (hyperplas* OR hamarto*)) OR Castleman* OR Castelman*):ab,ti) AND (chemotherapy/exp OR rituximab/de OR siltuximab/de OR tocilizumab/de OR 'monoclonal antibody'/de OR 'CD20 antibody'/de OR (chemotherap* OR rituximab OR (('cd 20' OR cd20 OR 'il 6' OR 'interleukin 6' OR il6) NEAR/3 (anti*)) OR siltuximab OR tocilizumab OR (monoclonal NEAR/3 antibod*)):ab,ti) AND ('clinical study'/exp OR 'cohort analysis'/de OR 'follow up'/de OR (clinical* OR cohort* OR longitudinal* OR (follow* NEXT/1 up) OR followup* OR prospective* OR retrospective* OR random* OR rct* OR placebo* OR ((double* OR single* OR triple*) NEAR/3 blind*) OR (controlled NEAR/3 stud*) OR trial*):ab,ti) AND [english]/lim

Medline (OvidSP)

("Giant Lymph Node Hyperplasia"/ OR (((angiofollicul* OR angiolymphoid* OR angiomat* OR "Giant Lymph") ADJ3 (hyperplas* OR hamarto*)) OR Castleman* OR Castelman*).ab,ti.) AND (Chemotherapy, Adjuvant/ OR "Antineoplastic Combined Chemotherapy Protocols"/ OR exp "Antibodies, Monoclonal"/ OR (chemotherap* OR rituximab OR (("cd 20" OR cd20 OR "il 6" OR "interleukin 6" OR il6) ADJ3 (anti*)) OR siltuximab OR tocilizumab OR (monoclonal ADJ3 antibod*)).ab,ti.) AND (exp "Clinical Trial"/ OR exp "Cohort Studies"/ OR (clinical* OR cohort OR longitudinal* OR (follow* ADJ up*) OR followup* OR prospective* OR retrospective* OR random* OR rct* OR placebo* OR ((double* OR single* OR triple*) ADJ3 blind*) OR (controlled ADJ3 stud*) OR trial*).ab,ti.) AND english.la.

Cochrane

((((angiofollicul* OR angiolymphoid* OR angiomat* OR 'Giant Lymph') NEAR/3 (hyperplas* OR hamarto*)) OR Castleman* OR Castelman*):ab,ti) AND ((chemotherap* OR rituximab OR (('cd 20' OR cd20 OR 'il 6' OR 'interleukin 6' OR il6) NEAR/3 (anti*)) OR siltuximab OR tocilizumab OR (monoclonal NEAR/3 antibod*)):ab,ti)

Web-of-science

TS=(((((angiofollicul* OR angiolymphoid* OR angiomat* OR "Giant Lymph") NEAR/3 (hyperplas* OR hamarto*)) OR Castleman* OR Castelman*)) AND ((chemotherap* OR rituximab OR (("cd 20" OR cd20 OR "il 6" OR "interleukin 6" OR il6) NEAR/3 (anti*)) OR siltuximab OR tocilizumab OR (monoclonal NEAR/3 antibod*))) AND (clinical* OR cohort OR longitudinal* OR "follow up" OR followup* OR prospective* OR retrospective* OR random* OR rct* OR placebo* OR ((double* OR single* OR triple*) NEAR/3 blind*) OR (controlled NEAR/3 stud*) OR trial*)) AND LA=english

Scopus

TITLE-ABS-KEY(((((angiofollicul* OR angiolymphoid* OR angiomat* OR "Giant Lymph") W/3 (hyperplas* OR hamarto*)) OR Castleman* OR Castelman*)) AND ((chemotherap* OR rituximab OR (("cd 20" OR cd20 OR "il 6" OR "interleukin 6" OR il6) W/3 (anti*)) OR siltuximab OR tocilizumab OR (monoclonal W/3 antibod*))) AND (clinical* OR cohort OR longitudinal* OR "follow up" OR followup* OR prospective* OR retrospective* OR random* OR rct* OR placebo* OR ((double* OR single* OR triple*) W/3 blind*) OR (controlled W/3 stud*) OR trial*)) AND LANGUAGE(english)

PubMed publisher

((((angiofollicul*[tiab] OR angiolymphoid*[tiab] OR angiomat*[tiab] OR Giant Lymph*[tiab]) AND (hyperplas*[tiab] OR hamarto*[tiab])) OR Castleman*[tiab] OR Castelman*[tiab])) AND ((chemotherap*[tiab] OR rituximab[tiab] OR ((cd 20*[tiab] OR cd20[tiab] OR il 6*[tiab] OR interleukin 6*[tiab] OR il6[tiab]) AND (anti*[tiab])) OR siltuximab[tiab] OR tocilizumab[tiab] OR monoclonal antibod*[tiab])) AND ((clinical*[tiab] OR cohort[tiab] OR longitudinal*[tiab] OR follow up*[tiab] OR followup*[tiab] OR prospective*[tiab] OR retrospective*[tiab] OR random*[tiab] OR rct*[tiab] OR placebo*[tiab] OR double blind*[tiab] OR single blind*[tiab] OR triple blind*[tiab] OR controlled stud*[tiab] OR trial*[tiab])) AND english[la] AND publisher[sb]

Google scholar

Castleman chemotherapy|rituximab|siltuximab|tocilizumab|"monoclonal|CD20 antibody|antibodies"|"anti il-6|interleukin-6|il6" clinical|cohort|"follow up"|prospective|retrospective|randomized|randomised|random|rct

REVIEW

Evidence-based medicine in older patients: how can we do better?

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ABSTRACT

Evidence-based medicine (EBM) aims to integrate three elements in patient care: the patient situation, scientific evidence, and the doctors' expertise. This review aims 1) to assess how these elements are systematically different in older patients and 2) to propose strategies how to improve EBM in older patients.

The ageing process systematically affects all three elements that constitute EBM. First, ageing changes the physiology of the older body, makes the patient more vulnerable with more multimorbidity and polypharmacy and affects somatic, psychological and social function. The heterogeneity of older patients may lead to overtreatment of vulnerable and undertreatment of fit older patients. Second, representative older patients are underrepresented in clinical studies and endpoints studied may not reflect the specific needs of older patients. Third, adequate clinical tools and schooling are lacking to aid physicians in clinical decision-making. Strategies to improve elements of EBM include: first systematically acknowledging that physical, mental and social function may reveal patients' vulnerability and specific treatment goals. Second, clinical studies specifically targeting more representative older patients and studying endpoints relevant to older patients are warranted. Finally, teaching of physicians may increase their experience and expertise in treating older patients.

In conclusion, in older patients the same elements constitute EBM, but the elements need tailoring to the older patient. In the clinic, a thorough assessment of individual patient preferences and physical, mental and social functioning in combination with increased level of experience of the doctor can increase the quality of EBM in older patients.

KEYWORDS

Ageing, elderly, evidence-based medicine, clinical studies, randomized controlled trials

INTRODUCTION

Older people are becoming a more prominent proportion of modern Western societies, both in absolute and relative terms. This is the result of increasing life expectancy, decreasing fecundity rates, and specific changes in population demographics, such as the baby boom after the Second World War. In Europe the number of inhabitants aged 65 years is 88 million (17% of total population) today and is projected to increase to 157 million (30%) in 2060 (Eurostat Statistics). As a result, a sharp increase in health care demand by older people is foreseen in the near future, which will affect nearly all domains of medicine.[1]

Evidence-based medicine (EBM) is the hallmark of modern medicine and aims to integrate the individual patient's situation, scientific evidence and the physician's experience and expertise in the process of clinical decision-making.[2] This review aims 1) to assess how the elements that constitute EBM are systematically different in older patients and how these differences affect the degree of EBM in older patients and 2) to propose strategies how to improve EBM in older patients.

CURRENT SITUATION

To come to strategies to improve EBM for older patients, we will first define the components of EBM. Then we explore

how the ageing process affects the physiology and function of the older body, how these physiological changes and altered patient situation affect the balance between cost and benefits of treatment decisions and how these aspects are addressed in current scientific evidence.

Evidence-based medicine

The term evidence-based medicine was introduced in the early 1990s and has been defined as the 'conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients'.[2] The essence of EBM is the complementary role of scientific evidence, physicians experience and expertise, and the individual patient's situation and preferences in clinical decision-making. In clinical practice these components cannot be assessed entirely separately. For instance, the doctor's opinion is strongly based on his assessment and interpretation of relevant literature and of the patient's situation.

Consequences of ageing

Ageing results from the accumulation of damage to the body due to internal and external stressors.[3] Accumulated macromolecular damage affects the functioning of cells and tissues, which compromises the body's capacity to maintain homeostasis thus causing an inherent increase in the chance of disease and death.[3] This definition of ageing mirrors our clinical observation of increased burden of disease and higher chance of mortality with increasing age in our patients.[4] There are several inherent consequences of the ageing process that make the older patient fundamentally different from the younger patient. First, compared with younger ages physiology in the older body is different.[5] Second, there is a higher degree of multimorbidity and polypharmacy.[6] Third, in the older patient a somatic disease often affects the intricate relationship between somatic disease and physical, psychological and social functioning.[6] All three aspects fundamentally change the way treatment strategies and scientific evidence should be assessed. These three aspects are elaborated upon below.

First, physiology of the older body is different than at younger ages. Well-known factors associated with ageing are a decreased renal function, liver function and altered body composition, which affect metabolism and clearance of pharmacotherapeutics.[7] Such changes necessitate careful dosing of medications in older patients, especially since there is a concomitant risk of drug-drug interactions in patients with polypharmacy.[8] However, besides these pharmacokinetic and pharmadynamic changes, observational findings concerning everyday clinical problems exemplify that the older patient differs from the younger patient. For instance, in the oldest old, having a high blood pressure is associated with longer survival,[9] which contradicts the common paradigm that in middle age, hypertension is a well-established risk factor for cardiovascular disease and mortality. Similar paradoxical findings of association with better survival have been made for high levels of cholesterol and subclinical hypothyroidism in those over 85 years.[10,11] Likely explanations for these findings include the fact that in old age biology may be different than at younger ages. For instance, in an 85-year-old the vasculature exhibits a higher degree of stiffness, therefore requiring a higher blood pressure to maintain adequate perfusion of organs, and high blood pressure may thus be interpreted as an adequate adaptive response of the body to counteract age-related changes to the vasculature.[12]

Second, with increasing age the prevalence of disease increases, resulting in a high proportion of elderly suffering from multiple chronic diseases.[13] Previous studies show that 55-98% of the elderly have two or more chronic diseases (i.e. multimorbidity).[13] Applying clinical guidelines for single diseases to older patients with multimorbidity leads to polypharmacy.[14] Furthermore, in those with polypharmacy, the risk of negative outcomes is increased. In one study from the Netherlands, it was estimated that 6% of all hospital admissions was related to negative effects of medication use, and that half of these were preventable.[15] It is very likely, that among these patients admitted to hospital, there is an overrepresentation of frail elderly people with multimorbidity and polypharmacy. Furthermore, Opondo and colleagues showed that one in five medications given to elderly patients in primary care is inappropriate.[16] Some clinical trial evidence suggests short-term benefit or at least lack of harm of medication withdrawal.[17]

Third, in older patients the intricate relationship between the four axes somatic disease and physical, psychological and social functioning is more apparent than at younger ages.[6] Physical function includes the level of physical activity and the ability to perform activities of daily living, such as dressing, cooking, bathing and doing the groceries. Psychological function includes cognitive performance, apathy and depression. Social functioning is determined by the presence of a spouse, outdoor social activities with friends and the level of support provided by children and the social activity of the patient. In case of severe illness in younger patients, such as oncology patients, it is already custom to measure functional capacity as a marker of patient vulnerability to assess whether the patient can endure intense treatments such as chemotherapy.[18] In older patients the intricate relationship is also present when disease is less severe, as multimorbidity and polypharmacy often affect multiple axes. Together, the four axes that characterise the older patient, may mark the extent of increased vulnerability, and may therefore serve as determinants of disease or treatment outcome. However,

the four axes could also be endpoints: for the older patient physical, psychological and social function largely determine the level of dependence and quality of life and may be affected by disease and treatment.[19] Thorough assessment of all axes is critical both in clinical studies of older patients as well as when treating an individual older patient.

In conclusion, physiology of the older body is different than at younger ages, there is a high degree of multimorbidity and polypharmacy and in the older patient physical, psychological and social function importantly determine disease and treatment outcome. Altogether, these consequences of the ageing process make the elderly patient more vulnerable for diseases and disease complications, affecting the physical, psychological and social function in the older patient. Treatment outcomes are strongly affected by these aspects, as they affect the balance between 'costs' and 'benefits' of treatment in the older patients.

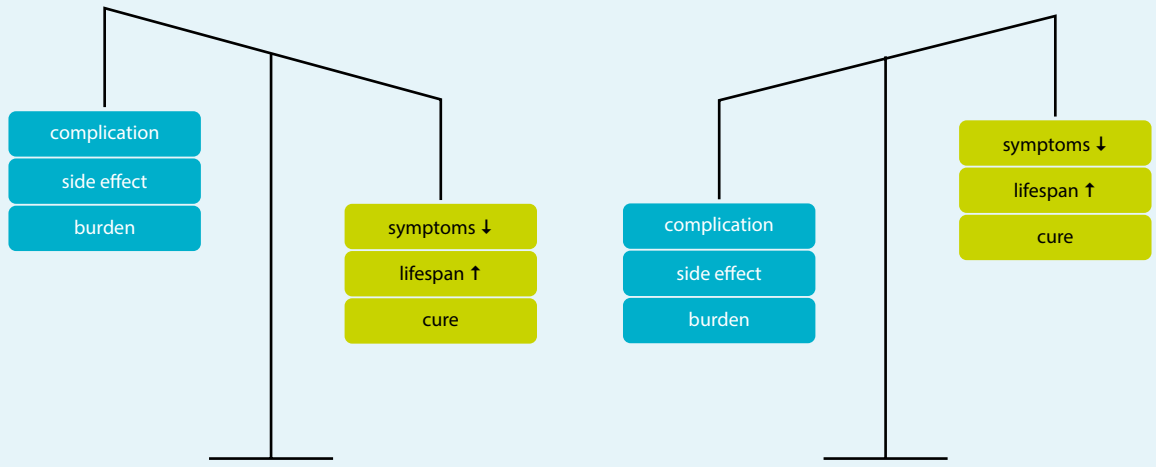
Balance between 'costs' and 'benefits'

The essence of making treatment decisions is the assessment of the balance of 'costs' and 'benefits' between different treatment strategies (*figure 1, left panel*). Positive treatment effects or 'benefits' (such as cure, symptom relief or survival) should outweigh the negative consequences or 'costs' (such as burden of treatment, risk of complications or side effects).

When compared with younger age groups, the negative effects ('costs') and positive effects ('benefits') of treatment are likely to be different in older patients. In general, the 'costs' will be higher and the 'benefits' lower (*figure 1, right panel*). Ageing leads to decreased physiological function, decreased capacity of the body to respond to perturbations and hence increased in vulnerability of the patient.[3] Therefore, older patients have higher risks of complications of medication, surgery and other interventions. For instance, inactivation and immobilisation result in loss of muscle mass, which in older age recovers more slowly than at younger ages and is a risk factor in its own right, for instance, for falls.[20] This may lead to long rehabilitation periods, functional decline and loss of independence.[21] In the perioperative phase older patients have an increased risk of delirium, which in turn is a risk factor for cognitive and functional decline in the postoperative period.[22] Furthermore, as pharmacodynamic and pharmacokinetics change in older age there is a higher chance of drug-drug interaction especially in the presence of polypharmacy. A higher dosage above the therapeutic range can lead to more side effects or dosing below the therapeutic range, leading eventually to undertreatment.[7]

On the other hand, expected benefits are – again in general – lower. With a shorter remaining life expectancy in older age, identical relative benefits on life expectancy are much smaller in absolute terms in older age. For instance, a 10% reduction in ten-year mortality risk is very relevant at the age of 40 years when life expectancy is over four decades or more, but less so at the age of 85 years when remaining life expectancy may be no more than five years based on high calendar age alone. Furthermore, when functional capacity in older age is limited by a combination of factors, such as neurological disorders, sarcopenia, osteoarthritis, treatment of only one of these factors will result in a smaller restoration of physical

Figure 1. *Balance between treatment 'costs' and 'benefits'*



Schematic representation of selected elements constitute the 'costs' and 'benefits' of treatment option. The left panel represents a 'positive' balance for a theoretical treatment option in a younger patient. The right panel represents a 'negative' balance for the same treatment option in an older patient as a result of the systematic higher chance of risks and complications and the lower gain of the treatment option

function compared with an individual in whom only one pathology limits functional capacity.

Arguably, the effect of treatments on endpoints is not only quantitatively different in older patients, they may also be qualitatively different. Older patients may value physical or social functioning as their most important determinant of quality.[23]

The degree to which this is relevant for the individual patient may vary greatly: patients of the same calendar age may be very different in biological age. Due to the large heterogeneity among older patients, generalising treatments based on calendar age may result in overtreatment of frail older patients and undertreatment of fit older patients. Overtreatment may result from automatic prescription of medications according to guidelines to patients with multimorbidity. Especially when the indications of these individual medications are not weighed against the lag time to benefit or effect on quality of life,[24] it is likely that polypharmacy may occur which is detrimental to the patients rather than beneficial. On the other hand, at least in some fields such as breast cancer, patients are withheld treatments based on calendar age alone, whereas data suggest that there is undertreatment in older patients.[25]

In conclusion, in older age the balance of cost and benefit of any medical treatment is in general less advantageous than at younger ages. However, large inter-individual differences exist and endpoints of interest may be different in older patients.

Scientific evidence in old patients

The different physiology, the increased level of multimorbidity and polypharmacy, and the multidomain functioning of the older patient constitute different requirements for clinical studies to be relevant for older patients compared with younger patients. Such requirements include the inclusion of representative older patients (i.e. including age-related physiological changes, multimorbidity and polypharmacy), the reporting and weighing of all four geriatric axes, and the inclusion of study endpoints that are relevant for older patients, such as physical, psychological or social functioning and quality of life. Clinical studies can be categorised in different domains: aetiological, prognostic, diagnostic, or intervention studies. Here we will explore whether these requirements are met for each of the different domains.

Dedicated aetiological studies are essential in understanding how health and disease work. Numerous large cohorts exist that specifically study health and disease in older age to understand how the ageing body works.[26,27,28] Typically these are observational studies, often hampering causal inference but providing testable hypotheses with respect to interventions to improve health and functioning. Aetiological studies performed in representative older patients may provide useful evidence for the treatment of older patients.

In clinical practice, several prognostic tools are being used to translate the individual patient characteristics into clinical advice. Well-known examples include the Framingham risk score for predicting cardiovascular risk,[29] Euroscore to predict mortality risk for cardiothoracic surgery,[30] and Adjuvant online,[31] an online tool to predict effects of different treatment modalities in patients with breast cancer. However, none of these three tools function well in older patients.[32,33,30] The systematic problem of these prognostic tools includes that they were not developed and validated in older populations and did not include data relevant to older patients, such as physical or cognitive function either as a prognostic factor or as outcome of treatment. There are very few clinically useful tools to assess vulnerability of the individual older patient, which carries the risk of generalisation of treatment advice. This may lead to systematic overtreatment of those who are considered fitter than they actually are and undertreatment of those who are fitter than considered generally.

Diagnosis of disease is not fundamentally different in older age compared with younger ages. However, the use of diagnostic tools may be different in several aspects. First, the a priori chances of a diagnosis may vary and hence the predictive value of a diagnostic tool may be different. For instance, the chance of an adrenal incidentaloma increases with age, but it is not always clear what the diagnostic approach or long-term follow-up should be.[34] Second, the burden of diagnostic tests for the patient may be higher. The preparation for a colonoscopy is troublesome in an older patient with mobility problems, increased fall risk or cognitive disorders. The indication for a colonoscopy in such a patient should be considered in the light of the indication, but also in light of the possible finding. If an operation for a potential tumour is not possible or desired by the patient, the burden of the colonoscopy may well outbalance the potential winnings. Third, it is unclear whether 'normal' values in old age are similar to younger ages. In older ages average haemoglobin and renal function are both below the normal range for younger patients. Sometimes these lower values are therefore considered 'normal for this age'. It is unclear whether this is true for all parameters. In the oldest old, for instance, haemoglobin levels below the normal limit is a common finding, but it is associated with increased risk of death.[35] In conclusion, diagnostic tools may perform differently in old age and applicability for the older patient should be assessed for each diagnostic tool in each setting separately.

Randomised controlled trials (RCTs) are considered the hallmark of EBM.[36] From all the different types of studies, RCTs or meta-analyses of multiple RCTs are regarded to have the highest 'level of evidence' and this drives clinical guidelines to formulate treatments based on the

results of these RCTs or meta-analyses of multiple RCTs. However, older patients are underrepresented in clinical trials as a result of selection by eligibility criteria.[37,38,39] The experimental design of randomisation reduces the chance of bias or confounding. From the researcher's perspective, including older patients in a clinical trial when studying the effects of a new treatment modality is not always attractive. Older participants introduce a higher burden of comorbidities and a higher rate of serious events that do not relate to the treatments that are compared. This 'competing risk' introduces an increased rate of randomness in the occurrence of endpoints, and therefore necessitates larger sample sizes and/or longer follow-up.[40] For similar reasons sometimes specific patient characteristics are required to study the effect of a drug that would result in exclusion of elderly participants from the study. For instance, to study the effects of a drug that is cleared by the kidney, a patient population may be required that does not include patients with renal failure. These inclusion criteria often select more implicitly in favour of younger participants. For instance, having an impaired renal function, defined as a clearance of 60 cc/min or more, is not a common finding in the oldest old, in which the average renal function is around 45 cc/min.[41] Finally, older participants are excluded for practical reasons: a trial protocol that requires participants to visit a study centre multiple times excludes older participants with mobility problems. Explicit exclusion criteria can be an upper age limit, or the exclusion of diseases (such as dementia) that are almost only seen in older adults. Notably, the reason for excluding patients based on age is not always justified when reporting the results.[38] As a result of these selection criteria, the elderly are underrepresented in RCTs. For instance, in a meta-analysis of RCTs performed in patients with acute coronary syndrome, among over 70,000 patients only 12% were aged over 70 years, whereas among prevalent cases this percentage is around 43%.[42] And when selection criteria made in RCTs regarding breast cancer treatment were applied to a clinical cohort of breast cancer patients, only 12% of patients could have been included.[43] Evidently, the older people who did participate in the RCTs could fulfil the selection criteria and are therefore not representative for the older population in general.[44] Endpoints in RCTs are often related to the incidence of disease and mortality, whereas for older patients the endpoints physical, psychological and social functioning may be considered more important.[23]

In conclusion, RCTs are the hallmark of evidence-based medicine, but for various reasons the elderly are systematically excluded. This leads to a quantitative underrepresentation of older adults and the older participants who are included are not representative for the general population of elderly people. Clinical guidelines are often written drawing on clinical trials in selected patients without comorbidities; therefore, external validity of these guidelines for older patients with multimorbidity is lacking. Endpoints studied by RCTs are not always relevant for older patients.

IMPROVING EBM IN OLDER PATIENTS

The level in which medicine for older patients is evidence-based can be increased by improving the contribution of each of the three elements to clinical decision-making. Below we will outline how the three elements of EBM can be improved: by systematically acknowledging the patient situation, generating more scientific evidence and increasing doctor's expertise with respect to EBM in older patients.

Systematic acknowledgement of the patient situation

The situation of the older patient should routinely be part of clinical practice as determinants of disease or treatment outcome. This starts with the awareness of the physician of the physical, psychological and social functioning of the patient and his/her preference with respect to the treatment goal. However, routinely performing a comprehensive geriatric assessment (CGA), in which all four axes of the older patient are thoroughly investigated in all patients above a certain calendar age, is likely not feasible or efficient in all situations, as it is very elaborate. CGA has been proven not to be effective, for instance, in the acute setting.[45] Furthermore, it is complex to derive specified clinical advice with respect to treatment of specific diseases from the CGA. Screening tools have been developed to assess the patient situation in a routine setting that include questionnaires assessing functional capacity, assessment of comorbidities and measurements of functional capacity (including cognitive function).[46] One of the most frequently used screening tools is the 'Fried Frailty Indicator' which defines frailty as the co-existence of at least three out of five potential symptoms: low gait speed, weight loss, self-reported exhaustion, low grip strength or low physical activity.[47] Gait speed in itself is also a robust prognostic marker for mortality risk.[48] Another approach to access frailty is to consider the burden of comorbidities. The most frequently used is the Charlson comorbidity index.[49] For large-scale clinical research CGA is not feasible either; rather, validated screening tools can be used. Such tools could serve as prognostics markers.[46] However, such screening tools have not found their way into clinical practice on a large scale, as they have not been tested and validated in clinical studies. Further studies are warranted to first design and validate screening tools and then to implement and test them for efficacy in routine care trajectories. Innovative approaches using modern technologies, such as internet and health sensors, may facilitate studying of important parameters such as

physical activity and cognition in large and heterogeneous populations.

Generating more scientific evidence

To increase the scientific underpinning of our everyday clinical practice, several measures can be taken. First, for specific diseases and guidelines, existing evidence can be assessed for validity for older patients in general and individual patients specifically.

Second, more information can be obtained by using already available evidence. Given the lack of large numbers of representative older adults in individual studies, pooling data from multiple studies (preferably by pooling individual patient data) may provide interesting evidence for the older patient without the necessity of repeating such trials. Successful examples of such pooling of data are the meta-analyses of several trials, assessing the effects of newly introduced novel oral anticoagulation drugs (NOACs), showing no additional risk in the use of these agents in older patients.[50] Third, more and more representative older patients should be included in clinical studies. It is impossible to replicate all RCTs performed in middle age for all individual older patients. The heterogeneity of this patient group as a result of multimorbidity would necessitate a large number of RCTs,[51] which is not feasible because of financial constraints. Furthermore, performing RCTs is a greater burden for the patients.

It is, however, possible to perform clinical studies that are relevant for the older patient and contribute to a higher level of scientific evidence. Designing clinical studies for older patients requires specific measures, such as measures to ensure inclusion of representative older patients, adequate phenotyping of their physical, psychological and social functional status and studying relevant endpoints. There are guidelines on how to perform a RCT specifically in older age.[52] It is, however, not feasible to repeat all clinical trials in old age. Therefore alternative study designs may be more attractive. An observation design may help to increase our understanding of the effects of the ageing process and therefore may inform treatment decisions. Studies may be tailored to overcome the unique barriers of participation of older patients.[53] However, caution is warranted with respect to causal inference, which can be overcome by genetic Mendelian randomisation studies.[54] When diseases are studied that are relatively rare, or when observational studies are small, pooling data in individual patient data (IPD) meta analyses can provide valuable insights.[55] Because repeating all RCTs for older patients is not feasible, alternative designs for intervention studies can be considered. For instance, the stepped wedge design uses an approach in which the effect of an intervention is assessed before and after implementation in clinical practice.[56] In this way, evidence can be obtained on effectiveness without the necessity to randomise individual patients. Another design is the regression discontinuity design.[57] In this design patients who fulfil a certain criterion (for instance a blood pressure above 140 mmHg) are given a treatment that is medically indicated and compared with the effects in patients with a low blood pressure who do not get the treatment. In this design, the number of included patients is higher compared with an RCT, but because treatment indication reflects common practice, it may be more feasible to obtain larger number of patients.

Increasing doctors' experience and expertise

There is a need for better teaching and training of medical doctors in their understanding of the specific needs of older patients. This requires knowledge of the pathophysiology of the ageing process and its implications for the effects of treatments. Older patients are a part of the practice of all doctors and specific attention for older patients is not restricted to the attention of geriatricians. In clinical practice the presence or absence of evidence specifically for older patients needs to be taken into account by the treating physician. Furthermore, the lack of evidence should be discussed with the patient in the light of the individual patient situation and preferences. The general lack of evidence in older age means that there is often not one single 'best' treatment option, and underscores the necessity of shared decision-making.[58] This requires specific teaching of physicians with respect to communication skills and attitude towards the older patient.

DISCUSSION AND CONCLUSION

Taken together, the ageing process systematically affects all three elements that constitute EBM: patient situation, scientific evidence and doctors' experience and expertise. This ultimately leads to a low level of EBM in older patients. Strategies to improve the level of evidence-based medicine in older patients include systematically assessing the patient, designing more studies specifically targeting or including more representative older patients and teaching of medical doctors about the ageing and the older patient.

The level of scientific evidence for the treatment of our older patients may never reach the level of that for younger patients, as it will be impossible to repeat all clinical studies for each individual older patient with his own unique combination of comorbidities and vulnerabilities. However, not only the level of scientific evidence can be improved substantially, but also the other elements of EBM: addressing the patient situation and teaching of doctors. Arguably, the patient situation and hence patient preference may also be more heterogeneous in older

patients, making the contribution of this element relatively more important than it is at younger ages and increasing the necessity to also teach doctors in 'shared decision making' in the light of absence of scientific evidence.

In conclusion, in older patients the same elements constitute EBM, but the elements need tailoring to the older patient. Given the paucity of clinical studies that are valid for older patients more clinical studies in representative older patients are warranted. In the clinic, a thorough assessment of the individual patient preferences and physical, mental and social functioning in combination with increased level of experience of the doctor can guide individualised treatment decisions.

DISCLOSURES

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ORIGINAL ARTICLE

Risk of rabies exposure among travellers

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ABSTRACT

Background: In recent years, requests for rabies immunoglobulin have increased at Amsterdam's Academic Medical Center's travel clinic. Travellers who received rabies pre-exposure prophylaxis (PrEP) before travel departure have immunological memory that can quickly be activated by timely booster vaccinations after possible exposure to rabies. PrEP alleviates the need for costly and scarcely available rabies immunoglobulin in case of exposure. This study describes which travellers are at risk of rabies exposure and would benefit from PrEP. The secondary aim was to specify which factors influence decision-making on taking PrEP.

Methods: We reviewed electronic patient files of travellers attending our clinic for rabies post-exposure prophylaxis between January 2009 and February 2014. Demographic and travel characteristics were compared with a sample of patients who were seen for pre-travel advice at our clinic. To assess which factors had influenced the decision to take PrEP, a questionnaire survey was conducted.

Results: A total of 161 travellers experienced animal-associated injury. Compared with travellers from the pre-travel database, more people travelled to Southeast Asia (49.5% vs. 30.9%, p = 0.035) for comparable time periods (median 21 vs. 21 days, p = 0.083). Transcutaneous injuries (type III) were common (73.9%), most often inflicted by dogs (45%). Only ten travellers (6.2%) had received PrEP. Barriers for PrEP were high costs and a short time interval between consultation and travel departure.

Conclusion: Travellers to Southeast Asia should particularly be informed about rabies and the possibility of PrEP. Long-term travel was not associated with a higher risk of rabies exposure.

KEYWORDS

Rabies, travellers, pre-exposure prophylaxis, KAP, post-exposure prophylaxis, Netherlands, Southeast Asia

INTRODUCTION

Rabies is a zoonotic viral disease causing fatal encephalitis in mammals, including humans.[1,2] Dogs are the main source of human infections. Rabies causes an estimated 55,000 to 70,000 deaths annually, most of which occur in rural parts of Africa and Asia.[2,3]

In developed countries, rabies mainly occurs among travellers returning from endemic areas.

Rabies is a rare disease in the Netherlands, with five reported cases in the past 50 years. However, three of these five patients were treated in our hospital in the past seven years, suggesting an increase of infections. The three patients seen most recently had acquired rabies in Kenya, Haiti and India, respectively, the other two in Indonesia and Morocco.[4-8] All died, a tragedy augmented by the fact that rabies is a vaccine-preventable disease. It is not uncommon for travellers to experience a bite or scratch from a potentially rabid animal. According to a recent review, a one-month stay in Southern Asia, Southeast Asia, Central America, South America or Africa is associated with 0.4% chance of experiencing an animal-associated incident (AAI).[9]

Active immunisation with rabies vaccine can be administered as pre- and post-exposure prophylaxis (PrEP and PEP, respectively). After high-risk (transcutaneous or mucosal) exposure in unvaccinated individuals, passive immunisation with rabies immunoglobulin is included in the PEP regimen. Individuals who received active PrEP have immunological memory that can be activated quickly with post-exposure booster vaccinations. This precludes the need for administration of rabies immunoglobulin in case of exposure, which is expensive and typically not available in endemic areas.[10]

In recent years, there has been an increase in consultations after high-risk exposures among unvaccinated travellers at our clinic, leading to an increase in the use of rabies immunoglobulin. These patients would have benefitted from PrEP. Therefore, it would be beneficial to specify those at risk of an AAI while providing pre-travel advice.

Previous studies identified travel to North Africa or Southeast Asia, young age, travel to visit friends or relatives (VFRs) or tourist travel as risk factors for AAIs.[11-20] Although these descriptive studies are illustrative, they only comprised post-travel surveillance. We compared demographic and travel related factors of those who returned after an AAI to the overall population seen at our pre-travel department. By including this denominator, we were able to compare relative risks. This made more objective identification of populations at risk of an AAI possible.

Furthermore, we described the exposure and management details of these AAIs. Other objectives were to investigate the knowledge of rabies among travellers and factors that influenced the decision to receive PrEP before travel departure.

METHODS

The Medical Ethical Committee of the AMC approved the study.

Primary and secondary outcomes

The primary outcomes were demographic and travel related factors associated with the occurrence of an AAI. The secondary outcomes were factors influencing the decision to take PrEP.

Data collection

Electronic patient files of travellers requesting PEP at the AMC between January 2009 and February 2014 were analysed to obtain demographic information (sex, age), travel details (duration, location, type of travel) and AAI related information. This includes time interval between departure and AAI, WHO risk classification, animal species involved in AAI, means of contact with an animal, location of injury, wound care, time interval between AAI and PEP, and rabies immunoglobulin availability at the local hospital. All travellers requesting PEP after experiencing an AAI while traveling abroad were included in this study. We excluded patients who requested PEP after an AAI that occurred in the Netherlands, because our focus was on travellers at risk.

In order to assess which demographic factors and travel characteristics were specific for travellers requesting PEP (PEP group), PEP group travellers who had obtained pre-travel advice were compared with a group of 1749 travellers seen at the pre-travel clinic prior to departure between 2011 and 2012 (pre-travel database). The PEP group were contacted to question whether they had obtained pre-travel advice. If individuals could not be reached but had been given vaccinations prior to this or previous similar travel, it was assumed they had obtained pre-travel advice.

Collection of demographic and travel related details of the pre-travel database travellers is described elsewhere.[21]

In order to complete missing data from the electronic patient files and to query travellers about the decision to take PrEP, a standardised questionnaire was administered. After providing informed consent, travellers included in this study were asked by either telephone or email to fill in an online survey made with Qualtrics (2005, Provo, UT, USA). The questionnaire included information on traveller's knowledge, attitude, and practice regarding rabies and rabies prevention. If data in the questionnaire contradicted those in the electronic patient files, the electronic patient file data were used. Travellers who had an AAI may have altered knowledge and attitudes toward rabies. To compare this in the PEP group to those who had not experienced an AAI, we used the same questionnaire in a convenience sample of travellers visiting our pre-travel clinic during 2013.

Definitions and measurements

To assess the severity of AAI, we used the WHO classification, which groups AAI into three categories: I (mild injury: contact with intact skin), II (moderate injury: minor scratches or abrasions without bleeding) and III (severe injury: transdermal exposure).[22]

The questionnaire aimed to identify factors that influenced travellers' decisions to take PrEP. These factors were based on elements of health behaviour models, experiences from our vaccination nurses and questionnaires in previous studies.[14,23-26] Factors included were: pre-travel advice, previous vaccinations, knowledge, perceived risk and perceived severity of infection, and barriers (vaccination costs and time interval between consultation and departure, perceived risk of side effects of PrEP). Travellers were asked to indicate the importance of perceived risk, perceived severity and barriers on the decision to take PrEP, on a scale from 1 to 6, 1 being not important and 6 very important.

Statistical analysis

All data analyses were carried out using IBM SPSS Statistics (version 20, Armonk, NY 2011). Pearson's chi-square test was used to compare the categorical variables 'sex' and 'travel destination'. The independent t-test was used to compare the continuous parametric variable 'age' and the Mann-Whitney U test was used to compare the non-parametric 'travel duration'. In order to assess whether questions investigating the decision to take PrEP could be combined, Cronbach's alpha was done to check internal consistency.

RESULTS AND DISCUSSION

Between January 2009 and February 2014, we treated 173 travellers with PEP after an AAI. Twelve individuals

were excluded: ten because the AAI had occurred in the Netherlands, two because they had been exposed to a rabid patient. Of the remaining 161 travellers, the mean age was 34.6 years (SD 17.1) and 84 (52.2%) were male (*table 1*).
Most travellers (119, 73.9%) experienced a severe (category III) incident and bites were the most reported means of contact (116, 72.0%). Dogs were involved in most incidents (72, 44.7%), followed by monkeys (48, 29.8%) and cats (21, 13.0%). Injuries occurred mainly on legs and hands (47, 29.2%; 44, 27.3%). The median time between departure and AAI was nine days (IQR 5-17 days) (*Appendix 1*).

Post-exposure care is prudent in the Netherlands and rabies immunoglobulin is not globally available

In principle, rabies immunoglobulin is not indicated for category I and II incidents or for those who have already received PrEP. In the PEP group, ten (6.2%) had a category I, 32 (19.9%) a category II and 119 (73.9%) a category III incident (*table 1*). Of the total 161 travellers, 94 (58.4%) received rabies immunoglobulin: 87 with a category III incident and seven with a category I incident. The reasons why these last seven patients received rabies immunoglobulin were that all had had contact with proven rabid pets imported to the Netherlands (one from Poland and one from Morocco) and that four were children under the age of 12 years, making their medical history less reliable. Of 119 travellers with a category III incident, 113 (95.0%) had not received PrEP and only 87 (77.0%) received rabies immunoglobulin. The reasons why rabies immunoglobulin was not administered in the remaining 26 travellers were either that the animal had been observed to be alive and healthy two weeks after the bite, or that more than seven days had passed since the initiation of PEP, and rabies immunoglobulin was not considered of additional benefit.
Of the total 94 rabies immunoglobulin administrations, only 17 (18.1%) were given at the travel destination, underlining the limited availability in the country of travel.[10]

Tourism and travel to Southeast Asia are risk factors for an AAI

Pre-travel advice had been obtained by 105 travellers in the PEP group. We compared these travellers to the pre-travel database (*table 2*). No differences were found in age, sex or travel duration. Travellers from the PEP group more often travelled as tourists (77.8% vs. 66.1%, p = 0.035), more often visited Southeast Asia (49.5% vs. 30.9%, p = 0.040) and did not visit Western Africa more often (4.8% vs. 12.9%, p = 0.128). The risk of AAIs for tourists has been described in several studies.[9,12,15,20,23] In contrast to these and our study, research from Marseille showed that VFR travellers heading to North Africa were predominantly at risk.[11] The lack of denominator data in terms of total number of departing travellers and associated relative risks (different travel clinics have different populations) could account for these differing results.
The frequent travel to Southeast Asia among travellers in the PEP group supports findings of earlier studies on PEP-requesting travellers,[13,15-20,27] and on rabies contracted among travellers.[28] Southeast Asia is one of the most popular travel destinations,[29] which may result in frequent reporting in post-travel surveillance studies. With the inclusion of denominator data (travellers seen for pre-travel

Table 1. *Exposure and management details of 161 travellers who experienced an AAI*

Sex: n (%)					
Male			84 (52.2)		
Age:					
Mean (SD)			34.6 (±17.1)		
Median (range)			32.0 (1-79)		
Pre-travel advice: n (%)					
Yes			105 (65.2)		
No			40 (24.8)		
Unknown			16 (9.9)		
Pre-exposure prophylaxis: n (%)					
Yes			10 (6.2)		
No			150 (93.2)		
Unknown			1 (0.6)		
RIG: n (%)	Category I (10)	Category II (32)	Category III (119)	Category III *no PrEP* (113)	Total (161)
Yes	7 (70.0)	0 (0.0)	87 (73.1)	87 (77.0)	94 (58.4)
No	3 (30.0)	32 (100.0)	32 (26.9)	26 (23.0)	67 (41.6)

AAI = animal-associated incident; PrEP = pre-exposure prophylaxis; RIG = rabies immunoglobulin.

Table 2. *Comparison of a database of 105 travellers that experienced an AAI to a database of 1749 travellers seen at the travel clinic*

	PEP indication	Pre-travel	p-value
Sex: n (%) 0.124[a]			
Male	53 (50.5)	802 (45.9)	0.356[a]
Female	52 (49.5)	947 (54.1)	
Age: 0.128[b]			
Mean (SD)	33.2 (±16.3)	36.5 (±17.9)	0.069[b]
Median (range)	30.0 (1-79)	35.0 (0-90)	
Reason for travel: n (%)			
Holiday/tourism	49 (77.8)	933 (66.1)	0.035[a]
VFR	3 (4.8)	299 (21.1)	0.195[a]
Business	3 (4.8)	179 (12.7)	0.612[a]
Other	8 (12.7)	338 (19.3)	reference
Not specified	42		
Travel destination: n (%)			
Southeast Asia	52 (49.5)	541 (30.9)	0.040[a]
South America	12 (11.4)	243 (13.9)	reference
Southern Asia	11 (10.5)	194 (11.1)	0.747[a]
Western Asia	4(3.8)	77 (4.4)	0.932[a]
Eastern Africa	7 (6.7)	168 (9.6)	0.726[a]
Northern Africa	2 (1.9)	43 (2.5)	0.939[a]
Western Africa	5 (4.8)	226 (12.9)	0.128[a]
Eastern Asia	4 (3.8)	63 (3.6)	0.672[a]
Central America	3 (2.9)	45 (2.6)	0.651[a]
Southern Africa	3 (2.9)	77 (4.4)	0.718[a]
Other	2(2.0)	62 (3.5)	0.581[a]
Travel duration:			
Median (IQR)	21 (12-28)	21 (14-30)	0.083[c]
Pre-exposure prophylaxis: n (%)			
Yes	10 (9.8)	119 (6.8)	0.287[a]
No	95 (91.2)	1630 (93.2)	

Other is Southern Europe (n=1 vs.3), Eastern Europe (n=1 vs.11), Central Africa (n= 0 vs.15), Caribbean (n= 0 vs.33). [a]Pearson's Chi-square test; [b]Independent T-test; [c]Mann-Whitney U test; [d]Travel duration was found in 79 electronic patient files; [e]Other; study and/or research, expatriate, voluntary/missionary. AAI = animal-associated incident; PEP = post-exposure prophylaxis; VFR = travel to visit friends or relatives.

advice), we show and confirm that travel to Southeast Asia is a risk factor for reported rabies exposure.

Surprisingly, despite our large West-African VFR population, we found a trend association of fewer PEP consultations among travellers to Western Africa. This could either be due to lower risks or, more probably, be the result of less awareness among this population, leading to unreported rabies exposure. Comprehensive and routine surveillance is often lacking in African countries and improvement remains crucial.[30,31]

The finding that travel duration of travellers in the PEP group did not differ from that of travellers seen for pre-travel advice suggests that long-term travel is not necessarily associated with an increased risk of reported AAIs. Several other studies have also shown that risk of AAI is not specifically associated with prolonged travel.[9,14,32,33] Therefore, the Netherlands' coordination centre of traveller advice (LCR) statement that PrEP should be considered when the intended duration of travel is at least three months must be considered for revision.[34]

Knowledge on rabies was generally good

To study knowledge of rabies and rabies prevention, 46 pre-travellers and 60 travellers returning after an AAI were interviewed, with comparable results (*table 3*). In both groups, most travellers were aware that dogs, bats and monkeys can transmit rabies, but very few travellers were aware that all terrestrial mammals are susceptible to rabies (5.0%). In both groups, all travellers but one were aware that rabies is transmissible through bites, whereas fewer knew of the risks of scratches and licks on broken skin. When asked how to prevent rabies infection, most were aware of vaccination (80% in both groups). A minority (13.3%) knew that wound disinfection could also prevent rabies.

Overall, both travellers in the PEP group and those interviewed prior to travel had good knowledge of rabies and how to prevent it. These results are comparable with

Table 3. *Questionnaire results of 60 travellers who experienced an AAI compared with 46 travellers seen for pre-travel advice*

	PEP-indicated (n = 60)	Pre-travel (n = 46)	p-value[1]
	n (%)	n (%)	
Which animals can transmit rabies?			
Dogs	52 (86.7)	44 (95.7)	0.181
Cats	22 (36.7)	27 (58.7)	0.031
Monkeys	45 (75.0)	33 (71.7)	0.825
Bats	50 (83.3)	37 (80.4)	0.800
In which ways can rabies be transmitted?			
Bites	59 (98.3)	46 (100.0)	1.000
Scratches	36 (60.0)	30 (65.2)	0.687
Licks on broken skin	31 (51.7)	26 (56.5)	0.696
In which ways can rabies be prevented?			
Vaccinations	48 (80.0)	37 (80.4)	1.000
Wound disinfection	8 (13.3)	--[2]	
Medicine	4 (6.7)	3 (6.5)	1.000
Avoiding animals	36 (60.0)	32 (69.6)	0.414
Vaccinating animals	43 (71.7)	8 (17.4)	0.250

[1]Fisher's exact test; [2]This possibility was not included in the multiple choice questionnaire of the pre-travel group; AAI = animal-associated incident; PEP = post-exposure prophylaxis.

previous knowledge, attitudes and practices (KAP) studies performed in France and among travellers to Southeast Asia.[14,23,24] Wound disinfection should be advised during pre-travel consultation as an easy and low-cost way to reduce risk of infection.

Pre-exposure prophylaxis should be scaled up

Importantly, of 161 travellers who experienced an AAI, only ten (6.2%) had received vaccinations before travel (*table 1*). This figure is comparable with previously recorded percentages ranging from 0-16% showing that there is ample room for improvement.[13,16-20,23]

Reducing vaccination costs and reducing the vaccination intervals could increase uptake

Questions exploring the decision to take PrEP among those who had experienced an AAI could not be analysed in groups due to a lack of internal consistency; therefore, all questions were analysed separately. On a scale of 1-6, the perceived risk of exposure to rabies was not rated as an important factor in the decision to take PrEP, (mean 1.98±1.00), whereas perceived disease severity scored high (mean 4.23±1.98). Vaccine costs and a short time interval between consultation and departure were rated as important barriers to the decision to take PrEP (vaccine cost: mean 4.30±1.62; time before departure: mean 4.00±1.94), whereas potential risks of adverse events scored lower (mean 2.43±1.28). No significant differences were found between travellers who took PrEP and those who did not (*Appendix 2*).

Reducing costs of the vaccination and reducing the vaccination intervals could be an important step in improving the uptake of rabies vaccinations prior to travel. Many previous studies have stated that costs were the main reason for travellers not to be vaccinated.[9,14,23,25] The limited timeframe was also mentioned before as a reason for not being vaccinated.[14,23] Intradermal schemes, although off-label in most developed countries, are effective and boostable.[35-38] We have previously proposed various promising shortened intradermal schemes,[39] which are currently being investigated.[40-43] Further study of these schemes is important in order to fast-track implementation in clinical practice.

LIMITATIONS

There were several limitations of this study. First, the population that we used as comparison to our case population in order to identity risk factors for an AAI was strictly of a different origin than the cases because the timeframe of inclusion differed. The pre-travel database population visited our AMC travel clinic prior to travel, whereas the PEP population may have visited another travel clinic prior to travel. However, we argue that the comparison is justifiable because demographic and travel characteristics are expected to be similar. By only including those who had obtained pre-travel advice at a travel clinic in the comparison, we aimed to rule out differences in preventive behaviour.

Second, the online survey was administered post-AAI, with a maximum of five years between AAI and survey. This may have resulted in memory bias when filling in the questionnaires. For this reason we used information from the electronic patient files when available.

CONCLUSION

The results of this study show that pre-exposure prophylaxis rates for rabies are low. Travel to Southeast Asia and travelling as a tourist are risk factors for rabies exposure. Long-term travel was not associated with higher risk of rabies exposure. Dutch travellers generally have good knowledge of rabies and how to prevent it. Tourists travelling to Southeast Asia should be advised to have rabies PrEP. Vaccination costs and a short time prior to departure remain barriers to vaccination.

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DISCLOSURES

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Appendix 1. *Exposure and management details of 161 travellers that experienced an AAI*

Sex: n (%) Male	84 (52.2)
Age: Median (range)	32.0(1-79)
Travel destination: n (%)	
Southeast Asia	67 (41.6)
South America	20 (12.4)
Southern Asia	14 (8.7)
Western Asia	13 (8.1)
Eastern Europe	12 (7.5)
Eastern Africa	7 (4.3)
Northern Africa	6 (3.7)
Western Africa	6 (3.7)
Eastern Asia	5 (3.1)
Central America	4 (2.5)
Western Europe	3 (1.9)
Southern Africa	3 (1.9)
Southern Europe	1 (0.6)
Other	0 (0.0
Animal involved in AAI: n (%)	
Dog	72 (44.7)
Monkey	48 (29.8)
Cat	21 (13.0)
Bat[b]	14 (8.7)
Other[c]	3 (1.9)
Unknown	2 (1.2)
Not applicable[a]	1 (0.6)
Contact with animal: n (%)	
Bites[d]	116 (72.0)
Scratches	25 (15.5)
Licks	12 (7.5)
Other[a]	1 (0.6)
Unknown	7 (4.3)
Body part of injury: n (%)	
Leg	69 (42.9)
Arm	64 (39.7)
Torso	8 (4.9)
Head	6 (3.7)
Unknown	14 (8.7)
Wound cleaning: n (%)	
Yes	76 (47.2)
No	9 (5.6)
No wound[d]	6 (3.7)
Unknown	70 (43.5)

Appendix 1. *Exposure and management details of 161 travellers that experienced an AAI*

Place of start post-exposure prophylaxis: n (%)			
1st injection at travel destination 1st injection in the Netherlands Unknown	81 (50.3) 79 (49.1) 1 (0.6)		
Place of RIG administration: n (%)			
RIG on travel destination RIG in the Netherlands Not applicable	17 (18.1) (10.6) 77 (81.9) (47.8) 67 (41.6)		
Time from departure to AAI: (n = 101)	9.0	0-492	5-18
Time from incident to PEP initiation:			
In travel destination (n = 62) In the Netherlands (n = 61) Total (n = 123)[e]	0.0 10.0 2.0	0-14 0-80 0-80	0-1 3-12 0-10
Time from incident to RIG administration:			
In travel destination (n = 15) In the Netherlands (n = 55) Total (n = 70)[f]	0.0 5.0 4.5	0-6 0-44 0-44	0-1 3-14 2-12

[a]Scratch on rock in bat cave; [b]Includes cases where no bat was sighted, but where bats were highly suspected; [c]Includes cases of rodent and coatis; [d]Includes two cases where wounds were suspected to be from animal bites; [e]In 123 of the 161 PEP cases, time from incident to PEP was registered;[f] In 70 of the 94 RIG cases, time from incident to RIG was registered.

Appendix 2. *Comparing factors influencing the decision to take PrEP of 60 travellers*

	Total: n (%)	**PrEP: n (%)**	**No PrEP: n (%)**	**p-value[b]**
Pre-travel advice Yes No	 44 (73.3) 16 (26.7)	 5 (100.0) 0 (0.0)	 39 (71.0) 16 (29.1)	0.199
Rabies mentioned in pre-travel advice Yes No	 22 (50.0' 22 (50.0)	 4(80.0) 1(20.0)	 18 (40.9) 21 (47.7)	0.172
Rabies vaccines mentioned in pre-travel advice: n (%)[a] Yes No	 26 (59.1) 18 (40.9)	 3 (60.0) 2 (40.0)	 15 (38.5) 24 (61.5)	0.325
Previous travel vaccines Yes No	 58 (96.7) 2 (3.3)	 5 (100.0) 0 (0.0)	 53 (96.4) 2 (3.6)	0.839
	Total: mean (SD)	**PrEP: mean (SD)**	**No PrEP mean (SD)**	**p-value[c]**
Knowledge score	8.20 (±2.30)	7.60 (±2.79)	8.25 (±2.27)	0.585
Perceived risk of exposure	1.98 (±1.00)	2.60 (±0.89)	1.93 (±1.00)	0.117
Perceived severity	4.23 (±1.98)	5.80 (±0.45)	4.09 (±2.00)	0.104
Barriers Vaccine costs Time before departure	 4.30 (±1.62) 4.00 (±1.94)	 5.20 (±0.84) 3.20 (±1.92)	 4.22 (±1.65) 4.07 (±1.94)	 0.259 0.374
Perceived risk of side effects of PrEP	2.43 (±1.28)	2.40 (±1.67)	2.44 (±1.26)	0.795

[a]The 44 travellers that received pre-travel advice; [b]Fisher's exact test (one-sided); [c]Mann-Whitney U test.

ORIGINAL ARTICLE

A national survey on the decision-making process of dialysis initiation in elderly patients

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ABSTRACT

Background: The decision-making process of dialysis initiation in the elderly involves different considerations compared with younger patients. Cognitive, functional and psychosocial issues are likely to be more important than standard prognostic factors. To assess the role of these issues in the decision-making process regarding dialysis initiation in the elderly, a survey was conducted among nephrologists in the Netherlands.

Methods: An internet-based survey was sent to all members of the Netherlands Federation of Nephrology.

Results: Out of 298 invited, 94 Dutch nephrologists responded to the questionnaire. Reaching consensus with the patient and relatives and early withdrawal are difficult issues in the decision-making process in elderly end-stage renal disease patients. Geriatric impairments were considered (very) relevant issues (varying from 7-10 on a scale from 1-10) in the context of dialysis initiation, with cognitive dysfunction being most relevant (median 10, range 6-10). The majority of nephrologists (56%) underlined the need for screening for geriatric problems when considering dialysis in the elderly. A total of 26% reported using some form of screening measurement for the determination of the presence of one or more geriatric impairments.

Conclusions: Although cognitive, functional and psychosocial issues are considered relevant items in the context of dialysis initiation in the elderly, systematic assessment of these items is not standard of care in nephrology practice. Future research is needed to determine whether a more systematic screening for the presence of geriatric impairments can improve the decision-making process.

KEYWORDS

Decision-making, dialysis, elderly, end stage kidney disease, frailty

INTRODUCTION

The process of decision-making concerning dialysis initiation in the elderly is complex and hard to capture in protocols. In elderly patients, bridging to transplantation is usually not an option and prolonging of life must therefore be carefully weighed against the expected quality of life on chronic dialysis. In the last decennium, increasing attention has been drawn to conservative care as an acceptable alternative in selected elderly patients with end-stage renal disease (ESRD).[1-3] The Renal Physicians Association and the American Society of Nephrology proposed forgoing dialysis in patients with a very poor prognosis, including those with high comorbidity, severely impaired functional status and severe malnutrition.[4] However, in elderly patients without these contraindications, the decision-making process of commencing dialysis remains challenging. Elderly patients treated with conservative therapy may spend less time in hospital compared with elderly patients receiving dialysis therapy and they are more likely to die at home or in a hospice instead of in a hospital compared with dialysis patients.[5] Although age has been included in prognostic models in dialysis patients,[2] other studies found that age per se was not associated with early mortality or withdrawal in the elderly.[6] Elderly patients may exhibit more comorbidities, and the prevalence of functional and cognitive impairments in this group is high.[5,7,8] Frailty,[9]

cognitive impairment,[10] comorbidities[11] and impaired mobility[12] have been shown to be of prognostic value for early mortality and hospitalisation in the dialysis population. Despite the growing proportion of older dialysis patients, few studies have focused specifically on their prognostic relevance in the elderly population.

In oncology, assessment of geriatric impairments, such as cognition, mobility, (instrumental) activities of daily living (ADL), mood, nutrition, comorbidities and social environment, before the start of therapy can aid in identifying patients at risk for chemotherapy-related toxicity[13] and postoperative complications in surgical oncology.[14] A systematic review showed that in six studies focusing on the effect of geriatric evaluation in decision-making in oncology, such a geriatric evaluation changed the initial treatment decisions in a median of 39% of patients. In approximately two-thirds of patients this resulted in a more conservative treatment plan.[15] A questionnaire among oncologists and oncology nursing specialists in the Netherlands revealed that geriatric evaluation was used in two-thirds of participants, although often not systematically due to a lack of time, or limited availability of geriatricians.[16]

Little is known about nephrologists' considerations in the decision-making process of dialysis initiation in the elderly. Previous surveys among nephrologists revealed that patient preference, the presence of severe conditions, vascular dementia and a poor physical functioning were important determinants in deciding to withhold dialysis.[17,18] To what extent other frequently encountered geriatric problems such as mood disturbances, ADL impairment, frailty and (mild) cognitive impairment influence the decision-making of nephrologists is not known. For this reason, a survey was conducted to assess whether these issues are evaluated systematically before dialysis initiation and whether nephrologists would consider further evaluation in the elderly supportive in the decision-making process.

SUBJECTS AND METHODS

An internet-based anonymous questionnaire for nephrologists was developed, focusing on the main issues related to initiation of dialysis in elderly patients derived from clinical practice and the literature.[17-20] The survey consisted of 25 questions (Appendix) about decision-making itself and the potential role of a geriatric assessment in this process. Data were collected on characteristics of the responding nephrologists, including years of experience and facility type, and demographics of the dialysis population. The survey took about 15 minutes to complete. In February 2014, all members of the Netherlands Federation of Nephrology (NfN), 298 nephrologists in total, were requested by email to respond to the questionnaire. With only a few exceptions, all registered nephrologists in the Netherlands are members of the NfN. No fee was paid to respondents. All responses were entered into SPSS statistical package version 22 (IBM SPSS Data Collection, Chicago, Illinois, USA). To compare for differences between groups, a Student's t-test was used for continuous variables; for nominal variables, the chi-square test was used. For not normally distributed variables a Mann-Whitney U test was used. All other results are presented as descriptive data.

RESULTS

Characteristics

A total of 94 nephrologists from the Netherlands filled out the questionnaire (response rate 32%). All types of dialysis care facilities (university hospital, (non) teaching hospital, commercial dialysis centre), from all regions of the country were represented. The mean age of the participants was 47 years (33-65 years). The characteristics of respondents and their dialysis population are presented in *table 1*. One-third of the respondents estimated that the majority of their prevalent dialysis patients are over 70 years of age. Of all ESRD patients over 70 years, respondents estimated that a median of 80% (range 10-100%) would eventually start renal replacement therapy; 40% of respondents had started dialysis in one or more nonagenarians. Mean age of the dialysis population did not differ significantly between facility type and region.

Decision-making concerning dialysis in the elderly

Opinions about the level of difficulty of decision-making concerning dialysis in the elderly differed widely (median score 4 (range 1-10) on a scale from 1-10). The process of decision-making almost always included consultation of a multidisciplinary team, consisting of a nephrologist, a specialised nurse, a social worker and a dietician (95%). In some clinics a psychologist, a spiritual worker or a pharmacist complemented the team. In 8% a geriatrician was involved on a regular or a consultative basis. When dialysis was considered unfavourable because of a poor prognosis, only 11% of nephrologists estimated that older patients would always accept the recommendations of the nephrology team for conservative care instead of renal replacement therapy, while 9% experienced elderly patients often insisted on starting dialysis despite a contrary recommendation.

Different strategies were chosen in a hypothetical case of a frail older patient, in whom dialysis initiation was considered unfavourable, but no agreement could be reached about conservative therapy. Six percent of the nephrologists would initiate dialysis, since the patient and family made a well-informed choice for this option. Ten

Table 1. *Baseline characteristics*

	Total (n = 94)
Age of nephrologist in years (median)	47 (range 33-65)
Female sex	42%
Years registered as a nephrologist (median)	12 (range 1-32)
Facility type	
University hospital	21%
Large hospital (> 600 beds)	38%
Average size hospital (400-600 beds)	25%
Small hospital (< 400 beds)	13%
Dialysis centre	3%
Amount of patients over 70 years old	
21-40%	12%
41-60%	36%
61-80%	25%
81-100%	3%
Predominance of elderly patients* (> 60%) per facility type	
University hospital	9%
Large hospital (> 600 beds)	48%
Average size hospital (400-600 beds)	26%
Small hospital (< 400 beds)	45%
Dialysis centre	50%
Elderly ESRD patients* starting renal replacement therapy (median)	80% (10-100)
Elderly ESRD patients* choosing conservative care (median)	10% (0-70)
Initiation of RRT when conservative care was advised in elderly patients	
Never	11%
Seldom	56%
Sometimes	24%
Often	9%
Oldest patient starting dialysis (median)	89 (range 79-96)
Percentage of nephrologist who had started RRT in nonagenarians	48%
	*Elderly patients: > 70 years old

ESRD = end-stage renal disease; RRT = renal replacement therapy.

percent would refuse to start dialysis, regardless of the patient's wishes, since dialysis might be harmful in this frail patient. Most respondents remained unconvinced of either option. They would consult colleagues (42%) or initiate a dialysis test session for 1-3 months (37%) before making a decision in this particular case. Five percent of nephrologists would consult a geriatrician.

Of all respondents, 64% estimated that within their own dialysis population early withdrawal (within 6 months) had occurred at least once in an elderly patient (*table 2*). The main reasons for withdrawal were lack of improvement in quality of life (30%) or decline of the general condition (24%). Less often mentioned were progression of comorbidities or newly diagnosed comorbidities (19%) or technical problems involving dialysis treatment (13%). In 9% of cases withdrawal occurred after a time-limited trial. Other reasons for early withdrawal are listed in *table 2*. In 77% of the cases of early withdrawal, this was not unexpected to the nephrologist involved. The most frequently mentioned reason for starting dialysis despite hesitations was the inability to reach consensus with the patient and/or relatives to choose maximum conservative management.

Factors included in dialysis decisions in elderly patients

Geriatric impairment was considered a (very) relevant issue and was always taken into account by nephrologists when deciding whether a patient would be eligible for dialysis (*figure 1*). On a scale from 1 (not important at all) to 10 (very important), cognitive impairment scored a median of 10 (range 6-10). Preference of the patient and family (median 10 (range 3-10)) and comorbidities (median 9, (range 5-10)) were also considered (very) relevant in decision-making by almost all respondents. Most nephrologists answered that they take into account impairments in activities of daily living (ADL) (median score 8, (range 2-10)), mood disturbances (median 7, (range 2-10)) and mobility impairment (median 7, (range 1-10)). The patients' age was

also considered relevant in decision-making, with a median score of 7 (range 1-10).

As reflected by the wide range, the opinions regarding these geriatric impairments and age were divided. Caregiver burden (median 6, (range 1-10)) was considered least relevant. In a fictive case of a frail elderly patient considering dialysis, age was considered less relevant than cognitive impairment, comorbidity and ADL impairment. Decision-making seemed to be most difficult for patients aged 76-90 years (median 4 (range 1-10)), and easier for younger and older patients (median 3 (range 1-10)). Yet, the differences per age category are small and the ranges are wide (*figure 2*). The wide range is most distinct in the youngest and the oldest age category, due to the fact that some physicians consider decision-making more difficult with ascending age (40%), whereas others (30%) considered it less difficult when patients get older. We could not explain those different patterns by age of the nephrologist, years of experience and type of dialysis facility.

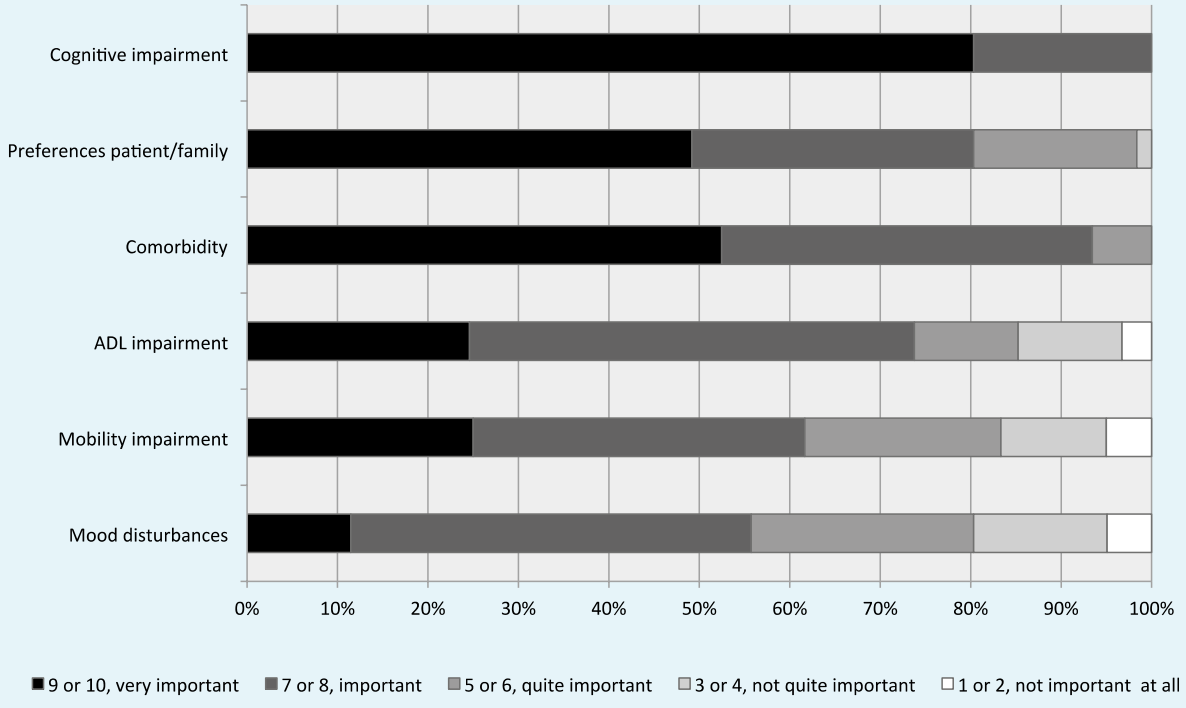
Additional evaluation of geriatric impairments

More than half of the respondents (56%) considered evaluation of geriatric impairments to be of potential benefit in the decision-making process before starting dialysis in elderly patients. Nephrologists in favour of a

Table 2. *Early withdrawal (< 6 months)*

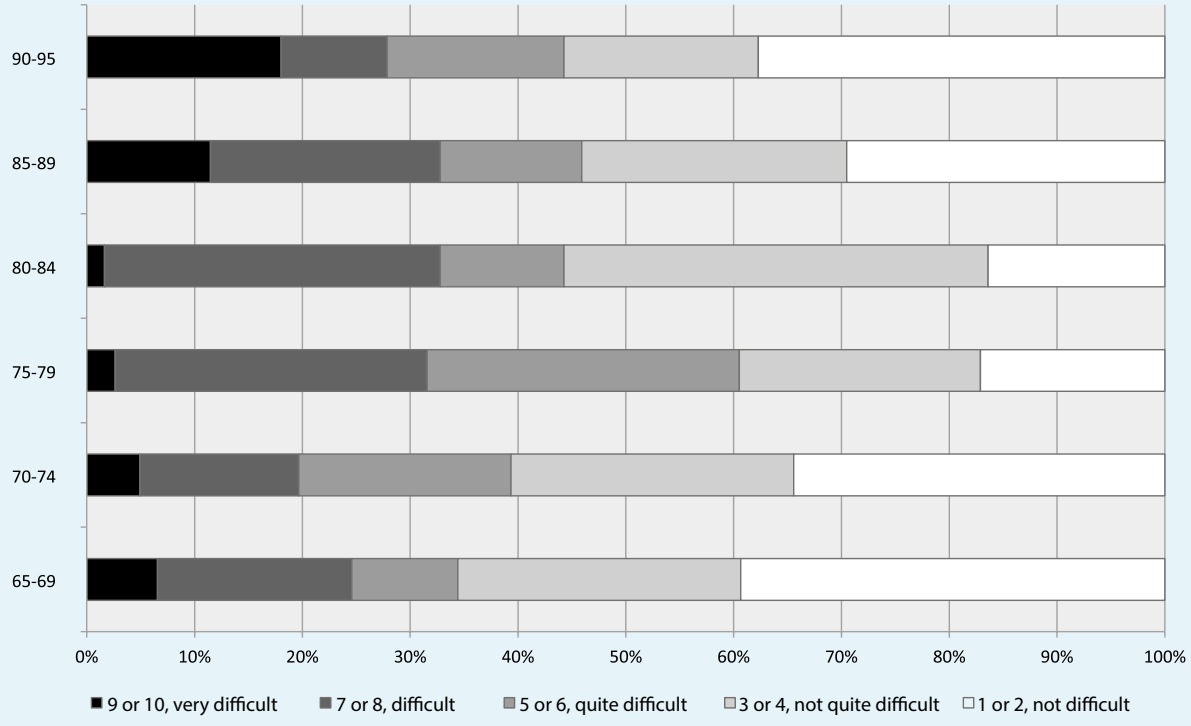
	Total (n = 72)
No. of nephrologists responded that withdrawal occurred at least once	**46 (64%)**
Surprised	*8 (19%)*
Not surprised	*33 (77%)*
Neutral	*2 (8%)*
Reasons for early withdrawal	**Total (n = 56)**
Lack of improvement in quality of life	17 (30%)
Decline general condition	13 (24%)
Progression of comorbidities	11 (19%)
Technical problems	7 (13%)
Evaluation after time-limited trial	5 (9%)
Difficulties in accepting the loss of self-reliance	1 (2%)
Decease of spouse	1 (2%)
Severe cardiovascular complications	1 (2%)

Figure 1. *Geriatric impairments taken into account in the decision-making process*



ADL = Activities of daily living.

Figure 2. *Difficulty of decision-making per category of age*



geriatric evaluation were generally younger (mean age 45.0 vs. 49.9 years, p = 0.02). This opinion was not influenced by gender. Arguments in favour of and against a geriatric evaluation are shown in *table 3*. Systematic evaluation of geriatric problems was expected to improve estimations about the condition after starting dialysis, which could help in informing the patient and his or her relatives (62%), in making one's own estimation of treatment success (47%) and in more often withholding dialysis in selected cases (11%). On the other hand, respondents found that different opinions between physicians could work counterproductively (33%) and it could be time consuming (19%). Of the nephrologists, 19% felt a geriatrician would lack sufficient knowledge regarding dialysis.

When asked about the ideal form of this evaluation, 78% of respondents preferred application of a short screening tool in the pre-dialysis clinic, supplemented with consultation of a geriatrician when needed while 23% preferred a comprehensive geriatric assessment, either performed by a geriatrician (18%) or a nephrologist (5%). Such an assessment was already performed as standard of care by 9% of respondents, while 26% of the respondents reported using one or more tools to assess one or more geriatric domains, most frequently focusing on cognitive impairments (e.g. the Mini Mental State Examination, MMSE) or frailty (*table 4*). Other geriatric impairments being tested were: impairments of ADL, depression, functional impairment, and mobility impairment.

DISCUSSION

This national survey revealed that geriatric impairments are considered important items influencing the decision-making process of dialysis initiation in the elderly, outweighing age as relevant item needing consideration. The majority of nephrologists (56%), especially younger colleagues, consider screening for impairments in the elderly population useful, but few use a geriatric assessment or screening instrument in the work-up of elderly pre-dialysis patients.

In general, decision-making in elderly ESRD patients was not considered difficult (median 4 (range 1-10)) but 89% of respondents at least occasionally reported difficulties in reaching consensus regarding treatment decisions. The 'Clinical Practice Guideline on Shared Decision-Making in the Appropriate Initiation of and Withdrawal from Dialysis' proposes to consider a time-limited trial when no consensus can be reached or the patient prognosis is uncertain.[19] However, the achieved quality of life after starting dialysis may not turn out as expected.[21] In a Canadian study of 584 ESRD patients (age 68 ± 14 years, mean time on dialysis 27 ± 22 months), 61% reported regretting their decision to start dialysis.[22] When looking at all cases of early withdrawal based on our survey, 77% were not unexpected to the responding nephrologist. This implies starting dialysis despite some hesitations about the benefits of dialysis is not exceptional. Worldwide,

Table 3. *Arguments in favour and against geriatric screening*

Arguments in favour of geriatric screening*	**n= 53**
Gaining more expertise to inform the patient and family about the expected condition after starting dialysis therapy	33 (62%)
Gaining more expertise to make the own judgment whether dialysis would be a good option	25 (47%)
Withholding dialysis in the right cases more often	6 (11%)
Make the decision-making process less time consuming overall	2 (4%)
More precise estimation of patients' condition	1 (2%)
Arguments against geriatric screening*	**n = 29**
Different opinions between physicians may cause confusion or 'overtreatment'	12 (33%)
Time-consuming, higher costs	7 (19%)
Doubts whether a geriatrician has enough knowledge of dialysis	7 (19%)
No evidence for a better prediction of outcome so far/ no positive experiences	3 (8%)
Decision should not be made based on cut-off value of a test	2 (6%)
Patients could feel they have to pass an exam before considered eligible	1 (3%)
False reassurance when the test results are good	1 (3%)
Could interfere with a good contact with the patients' general practitioner	1 (3%)
Not applicable for immigrants who do not speak Dutch	1 (3%)
Doubts whether it is a good predictor for quality of life	1 (3%)

*Respondents could give both arguments in favour or against

Table 4. *Geriatric assessment applied as standard of care*

	Total (n = 59)
No geriatric assessment applied	**40 (71%)**
Screening tool applied as part of standard care	**15 (26%)**
Cognition (e.g. mini-mental state examination)	12 (21%)
Frailty (e.g. Groningen Frailty Index)	8 (14%)
ADL impairment questionnaire (e.g. Katz)	6 (11%)
Depression (e.g. geriatric depression scale)	4 (7%)
Mobility impairment (e.g. Timed up and go, elderly mobility scale)	2 (4%)
Functional impairment (e.g. Lawton&Brody, Barthel Index)	1 (2%)
Comprehensive geriatric assessment applied	**5 (9%)**
Consultation geriatrician	1 (2%)
Screening for three or more geriatric impairments	4 (7%)
When considered necessary: geriatric consultation / screening tool applied	**4 (7%)**

ADL = activities of daily living.

based on the Dialysis Outcomes and Practice Patterns Study (DOPPS), most cases of withdrawal occur early after initiation of dialysis and account for 3-39% of deaths within the first 120 days, with a wide range between countries.[23] A time-limited trial may facilitate the decision-making process by postponing the definitive decision, but it will not prevent early withdrawal. These findings underline the need for a careful consideration of what to expect before the start of dialysis or a time-limited trial.

In our survey, cognitive dysfunction was considered most relevant of all geriatric impairments in treatment decision. Dementia is a known predictive factor for poor survival in patients initiating dialysis, with a two-year survival of 24% vs. 66% in patients without dementia ($p < 0.001$).[10] Cognitive impairment may compromise therapy adherence, diet and fluid restrictions, may lead to behavioural disturbances and higher care burden. Unexpected rapid decline of cognitive function was reported as a reason for early withdrawal, although this was not mentioned often (5%). Screening for cognitive function prior to dialysis initiation may help in obtaining an estimation of the patient's prognosis, the expected benefits of dialysis therapy and the risks of unwanted treatment outcomes.[8] A previous study found that cognitive impairment is largely underdiagnosed in dialysis and ESRD patients.[8] In our survey, only 21% of respondents reported using an objective instrument to assess cognitive function before dialysis initiation, although almost all considered it (highly) relevant to treatment decisions. A simple, validated test for cognition in the ESRD population is currently lacking. The Montreal Cognitive Assessment (MoCA), a brief cognition screening test, recently showed good sensitivity and specificity for cognitive impairments in prevalent dialysis patients and performed better than the better-known MMSE.[24] Whether this test will be of added value in decision-making for the elderly ESRD population is yet to be determined.

In addition to the disabilities previously mentioned to be relevant in the decision-making process,[17,18] such as comorbidity, vascular dementia and a poor physical

functioning, this survey shows mood disturbances and ADL impairment are also found to be relevant items needing consideration before starting dialysis therapy in the elderly. Depression is highly prevalent among dialysis patients, and undertreatment and underdiagnosis are common.[8] Both depression[25] and ADL impairment[26] are associated with adverse outcome in dialysis patients and early awareness might therefore be relevant in evaluating the patient prognosis, implementing early interventions and improving quality of life. As with cognition, it is not common practice to objectively assess these disabilities using a screening instrument. There were some initiatives (14%) to assess frailty, the phenotype of general decline in the ageing population.[27] Over the last decade, frailty has been recognised as a predictor for poor outcome in the dialysis population.[9] Although as yet no screening instrument has been validated for measuring frailty in the ESDR population, these initiatives may reflect the desire for a simple screening method for the overall condition in the elderly.

The present study has several limitations. The response rate of this nationwide survey was only 32%. This is a well-known issue in survey research. For example, previous international nephrology surveys yielded 50 or fewer responses in the Netherlands and other participating countries.[17,20] Responders and non-responders may differ in their interest in geriatric nephrology. This may have led to overestimation of the importance nephrologists seem to assign to geriatric impairments and the potential added value of screening for these impairments. A survey can provide only a simplified view of the complexity of daily practice. In an attempt to simulate real world decisions, this survey presented the questions concerning the importance of geriatric impairments in two different ways. For example, question 16, focusing on the value of the independent geriatric impairments, and question 19, incorporating geriatric impairments in a context of more complex decision-making, both showed geriatric impairments were considered more relevant than age itself in decision-making in elderly ESRD patients.

CONCLUSION AND POTENTIAL IMPLICATIONS

In this survey among Dutch nephrologists, geriatric impairments were shown to be considered relevant to the decision-making process regarding dialysis initiation in the elderly. Nephrologists are open for the use of screening instruments for geriatric problems, but structural, objective assessment of the presence and severity of geriatric impairments is not customary. This may be due to lack of validated screening tools in the ESRD and dialysis population. As geriatric impairments are associated with adverse outcome in dialysis, future research should focus on validating existing screening instruments in this patient population or developing new tools that take factors specifically relevant to renal disease and dialysis into consideration. In addition, it remains to be investigated whether the incorporation of some form of geriatric assessment in the decision-making process regarding initiation of dialysis will be useful in identifying vulnerable patients better suited for best supportive care.

DISCLOSURES

The authors declare no conflicts of interest. No funding or financial support was received.

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Appendix

Questionnaire

1. What is your age?
2. Are you a man or a woman?
3. How many years of experience do you have working as a nephrologist?
4. Does your hospital have a dialysis clinic?
5. What kind of hospital are you working at? (University, large (> 600 beds), medium (400-600 beds), small (< 400 beds), dialysis clinic)
6. In which province are you working?
7. How many of the patients in your pre-dialysis clinic are more than 70 years old?
8. How many patients older than 70 years who are eligible for dialysis actually start dialysis?
9. How old was your eldest patient starting dialysis?
10. How many of your patients older than 70 year who were eligible for dialysis choose to withhold dialysis?
11. How often do patients older than 70 years choose to start dialysis despite of your advice not to start dialysis?
12. Can you recall withdrawing dialysis within six months after the start of dialysis therapy in an elderly patient?

Yes

13. What was the reason for withdrawing dialysis in that patient?
14. Were you surprised the dialysis had to be cancelled this soon after the start? Please explain.

No

15. How difficult do you find it to make the decision on starting dialysis in the elderly? Please score each age category on a scale 1 (very easy) – 10 (very hard)
(Categories: 65-69; 70-74; 75-79; 80-84; 85-90; 91-95)

16. How often do you take next items into account when making the decision on starting dialysis? Please score each item on a scale 1 (never) -10 (always)
(Categories: Cognitive impairment, mobility impairment, age, ADL impairment, comorbidities, preference patient/family, care giver burden, mood)

17. Is the decision to start dialysis discussed for every patient in a multidisciplinary team?

18. What specialisations are represented in the multidisciplinary team?

Appendix

19. Which patient is most eligible for dialysis in your opinion? Please rank all patients from 1 (most eligible) to 6 (less eligible)
    a. A 85-year-old patient, few comorbidities, no cognitive impairment, no ADL disabilities
    b. A 80-year-old patient, few comorbidities, no cognitive impairment, ADL disabled
    c. A 75-year-old patient, many comorbidities, no cognitive impairment, no ADL disabilities
    d. A 80-year-old patient, few comorbidities, mild cognitive impairment, no ADL disabilities
    e. A 70-year-old patient, many comorbidities, mild cognitive impairment, no ADL disabilities
    f. A 75-year-old patient, many comorbidities, mild cognitive impairment, ADL disabled

20. Please choose your best option in this fictive case:
    An elderly, frail 88-year-old patient lives in a care centre and needs help with all his activities of daily living because of a lower leg amputation and cognitive impairment. He is diagnosed with terminal kidney failure. The patient's family is convinced dialysis is the best treatment option for him. The patient himself confirms that he wants to opt for dialysis. You are his nephrologist and discuss with patient and family the possible unfavourable effects on quality of life for this patient taking his frail condition into account. Nevertheless, the family still prefers to start dialysis. What would you do?
    a. You have no doubts. If the patient and family are well informed and still prefer to start dialysis, then you do so.
    b. You have no doubts. You think dialysis is not in the best interest of this patient. You tell the patient and family that you will not start dialysis (even if the family considers going to another dialysis clinic instead)
    c. You have your doubts whether dialysis is in the best interest of this patient. You consult your colleagues is this case.
    d. You have your doubts whether dialysis is in the best interest of this patient. You decide to start with a dialysis test session of one month, and afterwards decide whether dialysis should be continued.
    e. Other, namely...

21. Are there any validated screening tools used in your pre-dialysis clinic to assess the clinical condition of elderly patients? If so, which ones do you use?

22. Do you think a routinely performed geriatric assessment would be helpful in making the decision whether dialysis is convenient in an elderly patient?

23. What should be part of such a geriatric assessment in your opinion?
    a. A comprehensive geriatric assessment applied by a geriatrician/geriatric nurse
    b. A geriatric screening tool applied by the nephrologist with the possibility to consult a geriatrician if needed
    c. A comprehensive geriatric assessment applied by the nephrologist
    d. Other, namely...

24. What would you consider the added value of a geriatric assessment in the pre-dialysis population?
    a. Time-saving
    b. More expertise to inform the patient and family about the expected condition after starting dialysis therapy
    c. More expertise to make the own judgment whether dialysis would be a good option
    d. Withholding dialysis in selected cases

25. Could you think of an adverse effect of a geriatric assessment? If so, what effect?

26. In your pre-dialysis clinic, is there any form of collaboration with the geriatric department in assessing elderly patients with terminal kidney failure?

ORIGINAL ARTICLE

Is endoscopic nodular gastritis associated with premalignant lesions?

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ABSTRACT

Background: Nodularity on the gastric mucosa is occasionally seen in general practice. There is no consensus about the association of nodular gastritis and histological premalignant lesions. This study is designed to investigate the prevalence of histological premalignant lesions in dyspeptic patients with endoscopic nodular gastritis.

Methods: Consecutive patients with endoscopic nodular gastritis were compared with an age- and sex-matched control group. Endoscopic nodular gastritis was defined as a miliary nodular appearance of the gastric mucosa on endoscopy. Biopsy samples of stomach tissue were examined for the presence of atrophic gastritis, intestinal metaplasia, and dysplasia. The presence of *Helicobacter pylori* infection was determined by histology.

Results: From 5366 evaluated patients, a total of 273 patients with endoscopic nodular gastritis and 1103 participants as control group were enrolled. *H. pylori* infection was detected in 87.5% of the patients with endoscopic nodular gastritis, whereas 73.8% of the control group were positive for *H. pylori* ($p < 0.001$). Prevalence of incomplete intestinal metaplasia ($p = 0.016$) and dysplasia ($p < 0.001$) in patients with endoscopic nodular gastritis were significantly higher than in the control group. Prevalence of atrophic gastritis and complete intestinal metaplasia were also more frequent in patients with endoscopic nodular gastritis than in the control group.

Conclusion: Dysplasia, incomplete intestinal metaplasia and *H. pylori* infection are significantly more frequent in patients with endoscopic nodular gastritis. Although further studies are needed before a clear conclusion can be reached, we suggest that endoscopic nodular gastritis might serve as a premalignant lesion and could be biopsied in all patients for the possibility of histological premalignancy, in addition to *H. pylori* infection.

KEYWORDS

Atrophic gastritis, dyspepsia, dysplasia, intestinal metaplasia, nodular gastritis

INTRODUCTION

Gastric mucosal nodularity is an endoscopic finding occasionally seen in general practice. There is no consensus about the definite endoscopic definition of nodular gastritis and its clinical classification as an acute or chronic lesion.[1-10] The term endoscopic nodular gastritis is generally used as a miliary nodular appearance on the gastric mucosa on endoscopy.[1,2] Various terms such as antral nodularity,[3-7] antral nodular hyperplasia,[8] nodular antritis,[9] and micronodular gastritis[10] have been used for endoscopic nodular gastritis.

Endoscopic nodular gastritis is more common in areas with high prevalence of *Helicobacter pylori* infection. Many studies have shown that the prevalence of some types of gastritis such as endoscopic nodular gastritis is higher in *H. pylori*-positive cases in comparison with *H. pylori*-negatives.[6,7,10-12] However, some reports did not show any significant correlation between endoscopic nodular gastritis and *H. pylori* positivity.[2] There is also no consensus about the association of endoscopic nodular gastritis with histopathological changes such as

histological premalignant lesions.[1,2,6,7,9,12-14] For example although some studies has been revealed the association of endoscopic nodular gastritis and lymphoid follicle formation,[6,7,9] other studies did not show any correlation between them.[1,2,12] Association between endoscopic nodular gastritis and premalignant or malignant conditions as a pathological change is also not clear and there are a few published studies which have described this controversial association.[2,13-17]

Dyspepsia, which is a common heterogeneous group of abdominal symptoms, is used to characterise abdominal pain or discomfort centred in the epigastrium. Although the major cause of dyspepsia is a functional disorder, gastric cancer can also present with dyspepsia.[18,19] Gastric cancer, which is a major public health problem, is one of the most common causes of cancer-related mortality.[20,21] Mucosal chronic atrophic gastritis, complete or incomplete intestinal metaplasia, and gastric dysplasia are histological premalignant lesions.[22-24] A multistep cascade of precursors (superficial gastritis–atrophic gastritis–intestinal metaplasia–gastric dysplasia–carcinoma sequence) has been recognised for the development of the intestinal type of gastric cancer.[20]

Atrophic gastritis is characterised by the severe decrease or disappearance of typical gastric glands with the evidence of extensive inflammation.[25,26]

Intestinal metaplasia is a relatively frequent histological premalignant lesion and is defined as the replacement of the glandular gastric epithelium by mucosa that resembles the intestinal type cells. Complete intestinal metaplasia resembles a small intestinal epithelium phenotype with absorptive cells, Paneth cells, goblet cells, and a variety of endocrine cells. Incomplete intestinal metaplasia is diagnosed when the epithelium resembles the colonic phenotype with multiple, irregular mucin droplets of variable size in the cytoplasm and absence of absorptive cells.[25,27]

Gastric dysplasia is characterised by the decrease of cytoplasmic mucin, cellular pleomorphism, nuclear hyperchromatism, increased nuclear-cytoplasmic ratio, increased mitotic activity, and glandular disarray.[28]

Because there is no general consensus on the association of endoscopic nodular gastritis and histological premalignant lesions (e.g. atrophic gastritis, intestinal metaplasia, and dysplasia), we designed this study to find a possible connection. In this study a range of histological premalignant lesions were comparatively analysed between two groups of Iranian adult dyspeptic patients with and without endoscopic nodular gastritis.

METHODS

After obtaining the approval of the university ethical committee (93-01-13-8145) as well as written informed consent from each patient or his or her legal guardian in accordance with the Helsinki Declaration, all the consecutive rural patients with dyspepsia were recruited in this cross-sectional study between November 2011 and January 2014.

Diagnosis of dyspepsia was based on clinical findings. Endoscopic nodular gastritis was defined as a miliary nodular appearance on the antrum and/or body of gastric mucosa on endoscopy. All the endoscopic procedures were performed by an expert gastroenterologist with a high resolution white light endoscope. The biopsies were taken from all of the included patients with endoscopic nodular gastritis and normal endoscopy. Two biopsies from the antrum and two biopsies from the body were obtained from all patients with endoscopic nodular gastritis and the control group. Biopsy samples were fixed in 10% formalin and transferred to the lab in the appropriate condition. The staining with haematoxylin and eosin stain and Giemsa stain was done for histological detection of *H. pylori*. The samples were examined for the presence of atrophic gastritis, complete or incomplete intestinal metaplasia, and dysplasia by two expert pathologists who were blinded for the endoscopic findings.

The patients were excluded from the study if one of the following conditions existed: (a) patients in a poor cooperation; (b) history of *H. pylori* eradication; (c) history of use of proton pomp inhibitors, H2-receptor antagonists, antacids, non-steroidal anti-inflammatory drugs or antibiotics within the last two weeks prior to endoscopic evaluation; (d) history of gastric or oesophageal surgery; (e) any abnormality except nodular gastritis on endoscopy

Statistical analysis

Comparisons between the two groups were analysed by using the chi-square test for categorical variables and by t-test for continuous variables. Two-sided values of $p < 0.05$ were considered statistically significant. Statistical analyses were performed with SPSS 15.0. Odds of premalignant lesions were analysed by using logistic regression with adjustment by sex and age.

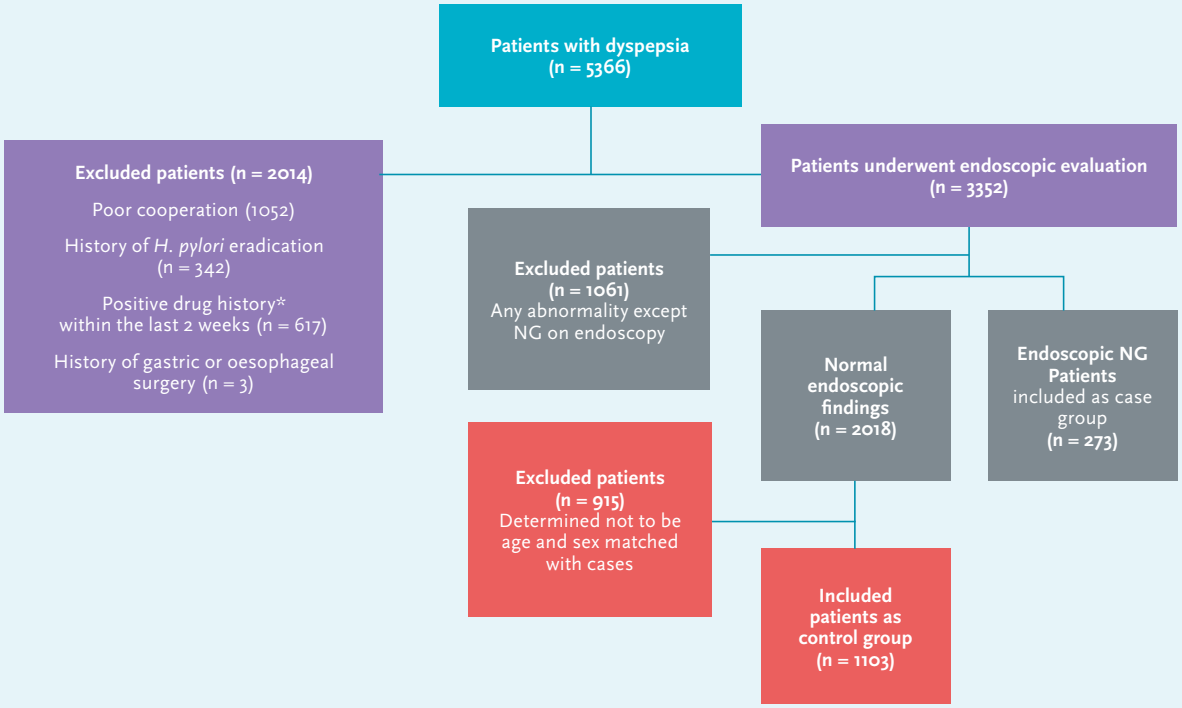
RESULTS

From 5366 evaluated patients, a total of 273 patients with endoscopic nodular gastritis and 1103 precipitants with normal endoscopic findings as a control group were evaluated (*figure 1*).

The mean age (SD) of patients with endoscopic nodular gastritis and the control group was 38.19±16.23 and 39.21 ±15.62 years, respectively. Of the patients with endoscopic nodular gastritis, 58.24% were in the age group 20-40 years and the majority of them (69.96) were woman.

Histological *H. pylori* infection was detected in 87.5% of patients with endoscopic nodular gastritis, whereas 73.8%

Figure 1. *Flow diagram for the patient selection process*



*History of use of proton pomp inhibitors, H2-receptor antagonists, antacids, non-steroidal anti-inflammatory drugs or antibiotics within the last 2 weeks prior to endoscopic evaluation; NG = nodular gastritis.

of the control group were *H. pylori* positive. The prevalence of *H. pylori* infection was significantly higher in patients with endoscopic nodular gastritis than in the control group (OR 2.31; 95% CI 1.72-3.70; p < 0.001) (*table 1*). In the *H. pylori*-positive subgroup the prevalence of premalignant lesions in patients with nodular gastritis was significantly higher than in the normal endoscopy group (16.3% vs. 7.9%, p = 0.000).

On histopathological examination, the rates of atrophic gastritis in patients with endoscopic nodular gastritis and the control group were 1.5% (4/273) and 1.3% (14/1103), respectively. Intestinal metaplasia (complete or incomplete) was detected in 4.4% of patients with endoscopic nodular gastritis but only 2.7% of the control group had evidence of intestinal metaplasia. Of the patients with endoscopic nodular gastritis, 2.9% and 1.5% had complete intestinal metaplasia and incomplete intestinal metaplasia, respectively. Of the control group 2.5% and 0.2% had complete intestinal metaplasia and incomplete intestinal metaplasia, respectively. The rates of dysplasia in patients with endoscopic nodular gastritis and control group were 9.9% and 2.8%, respectively (*table 2*).

The prevalence of dysplasia (OR 3.98; 95% CI 2.27-6.66; p < 0.001) and incomplete intestinal metaplasia (OR 8.63; 95% CI 1.47-45.00; p = 0.004) in patients with endoscopic nodular gastritis were significantly higher than the control group. On the other hand, atrophic gastritis (OR 1.18; 95% CI 0.38-3.60; p = 0.799) and complete intestinal metaplasia (OR 1.21; 95% CI 0.51-2.57; p = 0.716) were more frequent

Table 1. *The characteristics of the patients*

Variable	Patients with nodular gastritis; n (%)	Control group; n (%)
Gender		
Male	82 (30.04)	341 (30.92)
Female	191 (69.96)	762 (69.08)
Age groups (years)		
< 20	15 (5.50)	86 (7.80)
20-40	159 (58.24)	554 (50.23)
41-60	64 (23.44)	350 (31.73)
>60	35 (12.82)	113(10.24)
Total	273 (100)	1103 (100)
H. pylori infection	239 (87.5)	814 (73.8)

in patients with endoscopic nodular gastritis than in the control group, but the difference was not significant (*table 2*).

DISCUSSION

There are a few published studies that describe the association of histological premalignant lesions with endoscopic nodular gastritis. As far as we know, this study is the first report on a population of adult patients with dyspepsia in which a range of histological premalignant lesions were comparatively analysed between two groups of patients with and without endoscopic nodular gastritis.

In a case-control study Sokmensuer *et al.*[2] showed that intraepithelial lymphocytosis was significantly more prominent in patients with nodular gastritis and may contribute to nodule formation. In this study lymphoid hyperplasia was not more frequent in patients with nodular gastritis and the prevalence of *H. pylori* infection was not significantly higher than patients without endoscopic nodular gastritis. They showed that gastric dysplasia and complete metaplasia were more frequent in patients with nodular gastritis. They proposed that endoscopic nodular gastritis should be biopsied for the possibility of dysplasia and intestinal metaplasia.

A case-control study in dyspeptic patients in Kuwait showed that the prevalence of nodular gastritis was significantly higher in young women. They also showed that glandular atrophy (nodular gastritis 6.3%, controls 0%; p = 0.492) and intestinal metaplasia (nodular gastritis 3.1%, controls 0%; p = 1) were more frequent in patients with endoscopic nodular gastritis.[16]

In a case-control study, Dwivedi *et al.*[17] showed that atrophy (casess 25%, controls 5%; p < 0.05) and intestinal metaplasia (case 12.5%, controls 0%) were more frequent in patients with nodular gastritis. The mucosal inflammation was present in 93% of patients with nodular gastritis and 37.5% of the control group.

In a case-control study by Miyamoto *et al.*[13] nodular gastritis was predominantly seen in young women. The prevalence of lymphoid follicles was significantly higher in patients with nodular gastritis than in the control group. Gastric cancer was seen in 1% of the patients with nodular gastritis. They concluded that *H. pylori* eradication therapy should be considered for all patients with nodular gastritis for decreasing symptoms, risk of peptic ulcer disease, and possibly gastric cancer.

In another study, Nakashima *et al.*[29] showed that atrophy and intestinal metaplasia are rare but activity and chronic inflammation are severe in patients with nodular gastritis. Nodular gastritis was predominantly seen in the women, which tended to decrease in prevalence with the increase of patient age. All the patients with nodular gastritis were *H. pylori* positive.

A case-control study in Turkish adults showed that lymphoid follicle was not more prevalent in patients with nodular gastritis than in the control group. The prevalence of *H. pylori* was 65.4% and 59.2% among the patients with nodular gastritis and the control group, respectively.[1]

A cross-sectional study by Loffeld[30] in 305 consecutive patients with macroscopic signs of gastritis showed that the only sign with a high positive predictive value for *H. pylori* infection is antral nodularity.

In our series, similar to many other studies, the prevalence of *H. pylori* infection was significantly higher in patients with endoscopic nodular gastritis than in the control group (p < 0.001).[1,6,7,10-12,15,29-32] This result shows that *H. pylori* infection can be considered an effective factor to the formation of endoscopic nodular gastritis.

Most of our patients with endoscopic nodular gastritis were in the 3th and 4th decade of life (*table 1*) with a predominance for the female sex. These results, which are similar to other studies, showed that the prevalence of

Table 2. *Comparison of dyspeptic patients with and without endoscopic nodular gastritis (NG) regarding presence of histological premalignant lesions (PMLs)*

Histological findings	With NG; n (%)	Without NG; n (%)	p value *
Without PMLs	230 (84.2%)	1028 (93.2%)	<0.001
With PMLs			
Atrophic gastritis	4 (1.5%)	14 (1.3%)	0.799
Complete intestinal metaplasia	8 (2.9%)	28 (2.5%)	0.716
Incomplete intestinal metaplasia	4 (1.5%)	2 (0.2%)	0.004
Dysplasia	27 (9.9%)	31 (2.8%)	<0.001

*Comparisons between two groups were analysed by using the chi-square test.

endoscopic nodular gastritis was more common in young women.[13,15,16,29]

In this study atrophic gastritis, intestinal metaplasia, and dysplasia were more frequent in patients with endoscopic nodular gastritis. The prevalence of incomplete intestinal metaplasia (p = 0.004) and gastric dysplasia (p < 0.001) in patients with endoscopic nodular gastritis was significantly higher than in the control group. In this study, similar to some other reports, the prevalence of histological premalignant lesions was more frequent in patients with endoscopic nodular gastritis but at a more significant level (*table 2*).[2,16,17] These results show that endoscopic nodular gastritis may be considered a possible risk factor for the formation of histological premalignant lesions.

In this study, and some of the other reports, the *H. pylori* infection showed a significant increase in the endoscopic nodular gastritis,[1,6,7,10-12,15,29-32] on the other hand in many studies, the high prevalence of *H. pylori* infection in patients with histological premalignant lesions and cancer is described.[33,34] So *H. pylori* infection can be one of the possible mechanisms of increase in histological premalignant lesions in individuals with endoscopic nodular gastritis. Interestingly according to our results the prevalence of premalignant lesions in endoscopic nodular gastritis was also significantly higher than normal endoscopy in the *H. pylori*-positive subgroup (p = 0.000), which is in favour of a possible role for nodular gastritis in premalignant lesions.

Our study had some limitations. First, this was a single-centre study. Second, we evaluated only symptomatic patients. Third, we evaluated only rural participants. Fourth, we confirmed *H. pylori* infection with only one method.

In conclusion, we propose that incomplete intestinal metaplasia, gastric dysplasia and *H. pylori* infection is significantly more frequent in patients with endoscopic nodular gastritis. However, more studies should be done to the clarify the association between endoscopic nodular gastritis and histological premalignant lesions. Because of these significant correlations, we recommend that endoscopic nodular gastritis could be biopsied in all patients for the possibility of histological premalignant lesions such as intestinal metaplasia and dysplasia in addition to *H. pylori* infection.

DISCLOSURES

The authors declare no conflicts of interest. No funding or financial support was received.

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CASE REPORT

Spontaneous remission of acromegaly and Cushing's disease following pituitary apoplexy: Two case reports

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ABSTRACT

In this double case report, we present two special cases of pituitary apoplexy. First, we describe a patient with growth hormone deficiency despite clinical suspicion of acromegaly. Imaging showed evidence of a recent pituitary apoplexy, which might have caused spontaneous remission of the acromegaly before presentation at our outpatient clinic. Second, we describe a patient who presented with spontaneous remission of Cushing's disease after pituitary apoplexy, followed by a spontaneous remission of a relapse of the Cushing's disease due to a second pituitary apoplexy. These cases show that patients in spontaneous remission of hormonally active pituitary adenomas should be suspected of a pituitary apoplexy. Furthermore, even after spontaneous remission following pituitary apoplexy, careful long-term follow-up of these patients is mandatory, as relapses of hormonal hypersecretion can occur.

KEYWORDS

Acromegaly, Cushing's disease, pituitary apoplexy

INTRODUCTION

Pituitary apoplexy, defined as ischaemia or haemorrhage in the pituitary gland, occurs in 10-17% of pituitary tumours.[1,2] Clinical presentation is usually characterised by the acute onset of severe headache, visual field defects, meningeal irritation, ophthalmoplegia and hypopituitarism. Apoplexy primarily occurs in macroadenomas and most pituitary apoplexies occur in non-functioning adenomas.[3,4] We recently evaluated a case of clinically suspected acromegaly. To our surprise, low insulin-like-growth factor type 1 (IGF-1) levels were detected in this patient. Magnetic resonance imaging (MRI) showed evidence of a recent pituitary apoplexy, which might have led to spontaneous remission of the acromegaly. Furthermore, we recently treated a patient with Cushing's disease who showed two periods of spontaneous remission after subsequent pituitary apoplexies with disease recurrence in between.

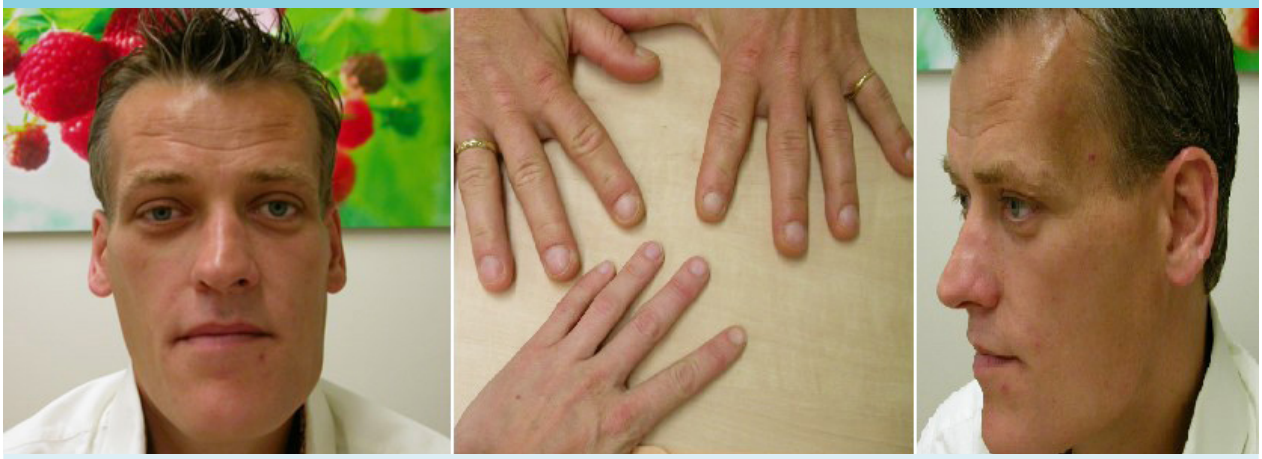
CASE REPORTS

Case 1

A 41-year-old male was referred to our tertiary referral centre in July 2011 with suspected acromegaly because of his distinct facial features and acral enlargement. The patient had a history of diabetes mellitus and insulin therapy since May 2009. He then started losing weight and achieved a weight loss of 24 kg in May 2011. In this period of two years, his blood glucose levels fully normalised and insulin therapy could be stopped. The patient was previously investigated by a maxillofacial surgeon because of dysgnathia due to asymmetrical elongation of the mandibula. The maxillofacial surgeon was the first to suspect acromegaly in this patient.

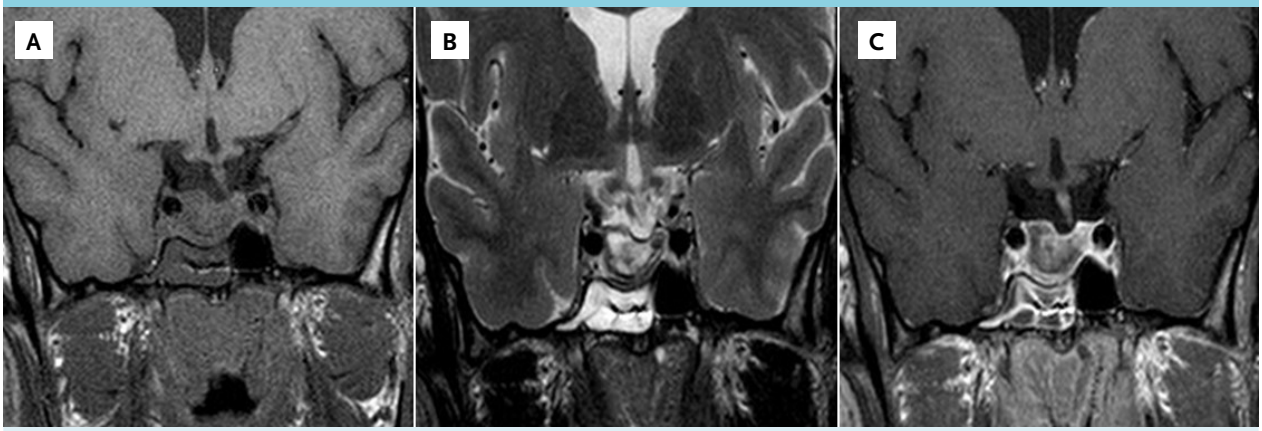
In April 2011, the patient experienced a sudden onset of severe pain in the neck, he did not have any headache. Since then, he complained of fatigue and he felt dizzy after standing up. His facial features had started to change five to ten years before. On physical examination, the acromegalic appearance was striking, characterised by bilateral asymmetric elongation of the mandibula, general asymmetry in facial appearance, the large nose, frontal bossing and large hands (*figure 1*). However, to

Figure 1. *Case 1 in July 2011*



1 The patient provided written consent for the publication of recognisable photographs
2 In the second picture, the lower hand belongs to the physician

Figure 2. *MRI of case 1 in June 2011*



MRI images show a space-occupying lesion in an enlarged sella on the right side, with a shift of the pituitary stalk to the left, iso-intense on T1 (2A), hyperintense on T2 (2B), and hypointense on T1 with gadolinium (2C). The lesion did not extend suprasellarly and the diaphragm is concave towards the lesion. Together these findings suggest an involution of a previously larger lesion due to apoplexy or necrosis. As a secondary finding an intrasphenoidal mucocele was seen.

our surprise, on laboratory testing he turned out to be growth hormone deficient (IGF-1 3.5 nmol/l (normal value (n) 11.2-32.8 nmol/l), growth hormone peak of 2.4 mU/l during insulin tolerance test (ITT)). In addition, hypogonadotropic hypogonadism was present (testosterone 0.2 nmol/l (n 11-45 nmol/l), follicle stimulating hormone (FSH) 0.74 U/l (n 1.5-11 U/l), luteinising hormone (LH) 0.82 U/l (n 1.4-8.5 U/l) and a partial adrenal insufficiency (cortisol peak during ITT 0.32 µmol/l.) Thyroid function was normal. MRI images revealed a space-occupying lesion in an enlarged sella at the right side, with a shift of the pituitary stalk to the left, iso-intense on T1, hyperintense on T2, and hypointense on T1 with gadolinium. The lesion did not extend suprasellarly and the diaphragm was concave towards the lesion. Together these findings suggest an involution of a previously larger lesion due to apoplexy or necrosis. As a secondary finding an intrasphenoidal mucocele was seen (*figure 2*). Because of these findings, we hypothesised the previous presence of a growth hormone-producing pituitary adenoma which was ameliorated by pituitary apoplexy. Repeated MRI imaging in July 2012 showed largely the same picture with signs suggestive of right-sided pituitary apoplexy (*figure 3*). During follow-up, IGF-1 levels normalised to 13.4 nmol/l (n 9.8-28.6 nmol/l). At this time the testosterone levels increased, but remained low (7.3 nmol/l (n 11-45 nmol/l)). No further dynamic testing of the pituitary adrenal axis has been performed up to now. Further follow-up was planned in order to screen for a possible relapse of the acromegaly.

The pituitary lesion was treated conservatively. The patient was further treated with testosterone and hydrocortisone therapy. The changes in the jaw even led to malocclusion

which caused the patient to have eating difficulties. This problem was surgically corrected.

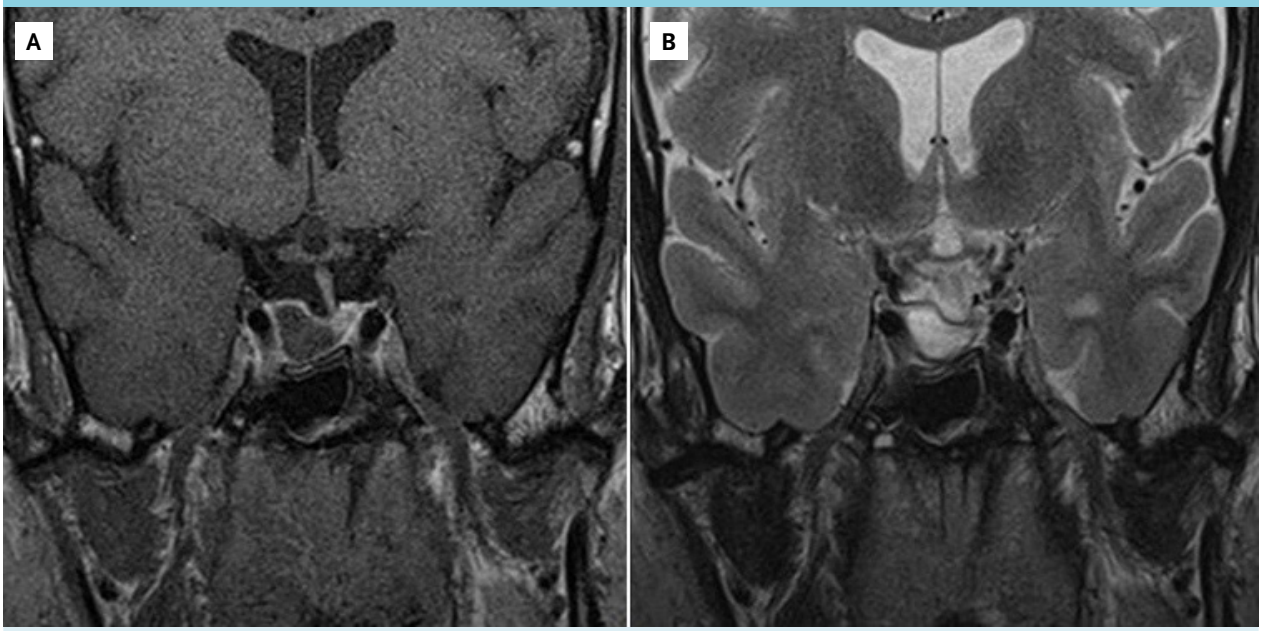
Case 2

The second patient was a 47-year-old female who was admitted to our neurosurgery department in September 2012 with acute severe headache. A computed tomography (CT) scan was performed in order to exclude a subarachnoid haemorrhage. Additional MRI scanning was performed when no subarachnoid haemorrhage was detected. Based on images of the MRI scan, pituitary apoplexy was suspected.

One year before she was diagnosed with diabetes mellitus type 2 and hypertension. Recently, she was analysed for hypercortisolism in another hospital previously to the episode of headache. She reported progressive muscle weakness, fatigue, weight gain of 30 kg in six months, the development of red stretch marks at the abdomen and easy bruising. In August 2012 her cortisol was not suppressed after low-dose dexamethasone (0.96 µmol/l). On physical examination, we noticed central obesity, moon face, supraclavicular fat pads, buffalo hump and abdominal purple striae. Laboratory results showed hypocortisolism (morning cortisol 0.04 µmol/l) and secondary hypothyroidism (free thyroxine 7.1 pmol/l (n 8-22 pmol/l), thyroid stimulating hormone 0.20 mU/l (n 0.4-4.0 mU/l)). The IGF1, LH, FSH and oestrogen levels were within the normal range. MRI images showed a space-occupying lesion at the right side, with a shift of the pituitary stalk to the left and an inhomogeneous area, predominantly hyperintense on T1 (*figure 4A*), hypointense on T2 (*figure 4B*).

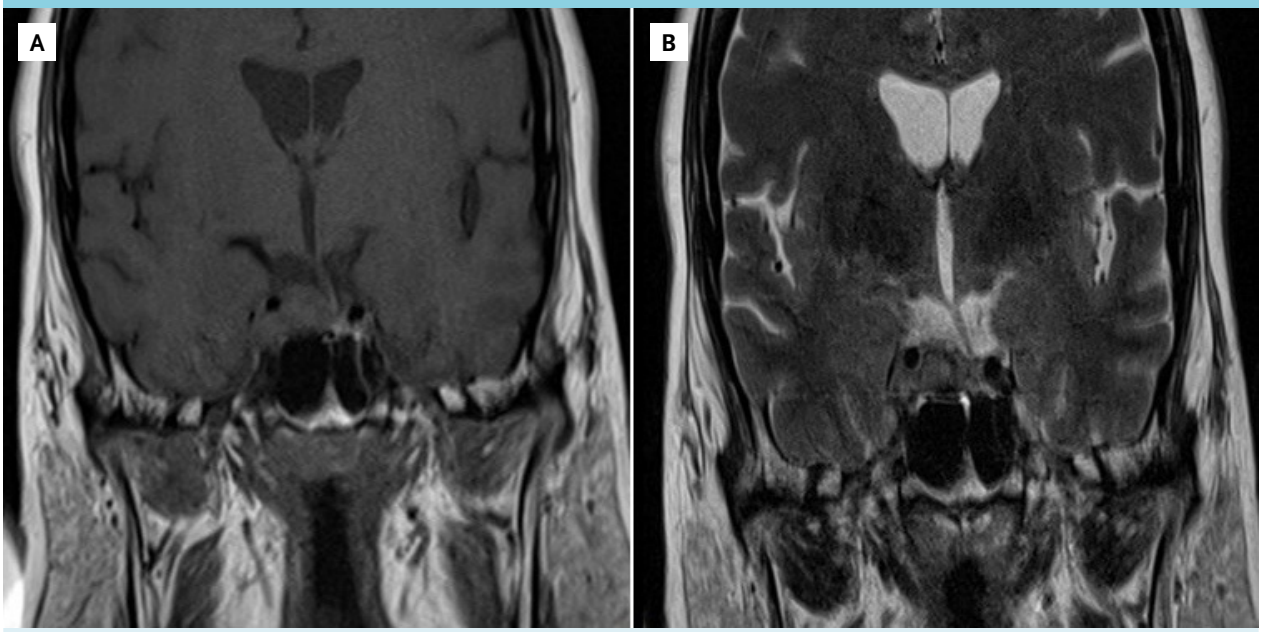
We hypothesised that this patient had previously suffered from a hormonally active pituitary adenoma which had caused Cushing's disease, which had now ameliorated after pituitary apoplexy. Hormone substitution therapy was started and the patient was regularly monitored at our outpatient clinic. During follow-up the hydrocortisone dose could gradually be tapered and was eventually stopped in April 2013. At that time, the pituitary-adrenal axis appeared to be fully recovered as was supported by repeated normal midnight salivary cortisol levels and normalised 24-hour urine cortisol levels. In May 2013, the patient started complaining of fatigue again and gained 7 kg of weight. In October 2013, the serum cortisol was not suppressed after low-dose dexamethasone (0.17 µmol/l). However, her urinary cortisol excretion and salivary cortisol were completely normal. At the time of testing the patient was not on any medication that could interfere with the dexamethasone suppression test. The 1 mg dexamethasone suppression test was repeated in February 2014 and the serum cortisol turned out to be 0.37 µmol/l. This was a strong indication that her Cushing's disease had recurred. Another evaluation of 24-hour urinary cortisol excretion was planned. However, in March 2014, the patient was brought into our emergency department with an acute onset of severe headache and visual impairment. MRI imaging showed a second pituitary apoplexy in the

Figure 3. *MRI of case 1 in July 2012*



MRI images show a right-sided intrasellar, T1 hypointense (3A), T2 hyperintense (3B), space-occupying lesion. This lesion shows more homogeneity compared with the first MRI and is suggestive of an intrasellar cyst as a sign of previous apoplexy or necrosis.

Figure 4. *MRI of case 2 in March 2014*



MRI images show a space-occupying lesion on the right side, with a shift of the pituitary stalk to the left. We can see an inhomogeneous area with a predominantly hyperintense on T1 (4A), hypointense on T2 (4B) which is a clear sign of pituitary apoplexy.

right side of the pituitary characterised by right-sided inhomogeneity, hyperintense on T1, spreading towards the right cavernous sinus (*figure 4*). After this second episode of pituitary apoplexy, the symptoms of hypercortisolism diminished and the 1 mg dexamethasone suppression test normalised (cortisol 0.04 µmol/l). Because the bleeding did not compress the optic chiasm it was decided not to perform surgery in the acute setting. Instead it was decided to perform elective endonasal endoscopic transsphenoidal surgery in September 2014 in order to remove the haematoma and remaining adenoma tissue to prevent disease recurrence in the future. Pathological examination of the removed tissue revealed typical adenoma tissue with adrenocorticotropic hormone (ACTH) expression.

DISCUSSION

Prior to his referral, the first patient most likely had acromegaly due to a growth hormone-secreting pituitary adenoma. This hypothesis is based on his striking physical appearance and on the MRI findings. Nevertheless, detailed endocrinological evaluation demonstrated apparent cure of acromegaly and even a transient growth hormone deficiency, most likely due to an acute mass effect of the pituitary apoplexy. The clinical findings in pituitary apoplexy vary widely and in this patient this event seems to have occurred 'silently' in the period between May 2009 and April 2011.[5] Pituitary apoplexy usually occurs spontaneously, as the neovasculature of a tumour is fragile, but it can be associated with a variety of events, including head trauma,[6] medications,[1] and dynamic pituitary function testing.[7,8] However, the exact pathophysiological mechanisms in these associations remain to be elucidated. Interestingly, diabetes mellitus has been associated with infarction of the normal pituitary gland due to its detrimental effects on the microvasculature of the pituitary. Our first patient had diabetes mellitus, which disappeared, possibly due to the remission of acromegaly after pituitary apoplexy. This can be explained by the fact that acromegaly is associated with insulin resistance.[9] Substantial lowering of growth hormone levels after pituitary apoplexy has been described before,[10] and even spontaneous remission of acromegaly has been reported.[11] However, growth hormone deficiency after pituitary apoplexy in acromegaly has never been reported before.

The second patient presented with a remission of Cushing's disease due to pituitary apoplexy, followed by a period of glucocorticoid deficiency, and a relapse of the Cushing's disease one year later. Remarkably, six months after the relapse, she again went into remission after a second pituitary apoplexy. Similar cases of remission after pituitary apoplexy followed by relapsing of Cushing's disease have been described previously.[12-14] However, this is the first case report describing a second pituitary apoplexy after relapsing Cushing's disease. Of note is the short period of glucocorticoid deficiency and remission of just one year before the relapse of Cushing's disease, which was, together with the prevention of a third

apoplexy, a reason to decide to surgically remove the pituitary lesion.

In conclusion, patients in spontaneous remission of hormonally active pituitary adenomas should be suspected of a pituitary apoplexy. Furthermore, even after spontaneous remission after pituitary apoplexy, careful long-term follow-up of these patients is mandatory, as relapses of hormonal hypersecretion can occur.

DISCLOSURES

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CASE REPORT

Interplay of co-inherited diseases can turn benign syndromes in a deadly combination: haemoglobinopathy and bilirubin transport disorder

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ABSTRACT

We present a case about a 25-year-old male patient suffering from a rare genetic disorder called Mizuho haemoglobin. He was admitted to the Intensive Care Unit with acute liver and renal failure. During admission he also developed a cardiac tamponade twice. Finally he received a liver transplantation. Hereafter the patient stabilised and his liver and renal functions improved. His symptoms could not be explained solely by his known disease. After searching the literature, similarities between his symptoms and a rare complication of sickle cell disease were found. Molecular diagnostics showed that the patient also suffered from Gilbert's syndrome. Due to his chronic haemolysis, symptoms of this other disease were masked. This stresses the importance of always looking for other causes if symptoms or changes cannot be explained by a known rare disorder.

KEYWORDS

Haemoglobinopathy, liver transplantation, bilirubin, Mizuho, Gilbert, hyperbilirubinaemia

INTRODUCTION

A patient with a known rare haemoglobinopathy was admitted with symptoms of fulminant hepatic failure requiring liver transplantation. He appeared to have a combination of two interacting genetic mutations. Molecular diagnostic possibilities have grown enormously in the past decades. As a consequence, more rare inherited diseases are diagnosed. Due to this, knowledge about these diseases is difficult to obtain, even with modern literature availability. Syndromes previously diagnosed based on clinical criteria can now be diagnosed even if the symptoms are obscured by concomitant diseases. We describe a case report of a patient with two rather benign single nucleotide polymorphisms (SNP); one very rare and one more common, but in combination leading to severe complications.

CASE PRESENTATION

A 25-year-old male was transferred from another hospital to our intensive care unit (ICU) with acute liver and renal failure to evaluate the possibility of acute liver transplantation. He had been diagnosed by DNA analyses with Mizuho haemoglobin as a child,[1] which is a rare disease of which only three other patients have been described in the world.[2-4] In this de novo heterozygous T→C mutation there is a Leu→Pro substitution at position 68 of the β-chain. This type of haemoglobin has higher oxygen affinity and the β-chain is unstable. It is associated with chronic haemolysis. A cholecystectomy was performed for symptomatic cholelithiasis at the age of 4 and a splenectomy at the age of 6 in an attempt to reduce haemolysis. After this last operation his transfusion need diminished. During his entire life the transfusion load was approximately 40 units of concentrated red blood cells with the majority given before the splenectomy. Until then

Table 1. *Laboratory results*

	U (Normal)	Admission	Before LT	ICU Discharge
Leucocytes	10^9/l (4-10)	41.3	21.5	13.4
Haemoglobin	mmol/l (8.7-10.6)	4.6	8.7	5.3
Haematocrit	v/v (0.42-0.52)	0.214	0.377	0.251
Thrombocytes	10^9/l (150-350)	131	134	70
CRP	mg/l (0.0-5.0)	70	54	51
Sodium	mmol/l (135-145)	133	135	136
Chloride	mmol/l (97-107)	99	99	101
BUN	mmol/l (2.5-7.5)	40,0	8,1	9,7
Creatinine	µmol/l (0-110)	638	77	204
ALP	U/l (0-120)	364	601	310
LDH	U/l (0-250)	1331	319	191
ASAT	U/l (0-40)	183	152	38
ALAT	U/l (0-45)	63	124	118
Total bilirubin	µmol/l (0-17)	1613	432	42
Direct bilirubin	µmol/l (0-5)		395	36
Calcium	mmol/l (2.20-2.60)	1.92	2.34	1.76
Phosphate	mmol/l (0.70-1.50)	2.37	0.47	0.76
Total protein	g/l (60-80)	54	55	37
Albumin	g/l (35-50)	29	23	23
Gamma-GT	U/l (0-55)	126	228	387
Glucose	mmol/l (4.4-5.5)	5.1		6.6
PT	sec (9.0-12.0)	15.6	12	12
APTT	sec (23-33)	124	36	37
Fibrinogen	g/l (1.7-4.0)	5.1	4	2.4
pH	(7.35-7.45)	7.24	7.43	7.43
pCO_2	kPa (4.6-6.0)	3.6	5.1	5.7
HCO_3	mmol/l (21-25)	11	25	28
Lactate	mmol/l (0.5-1.6)	0.6	0.7	0.9
Haptoglobin	g/l (0.3-2.0)	<0.2	0.5	0.6
Ammonia	µmol/l (15-45)	81		

his total and mostly conjugated bilirubin levels were around 200 µmol/l, due to which his jaundice was striking. He had no other signs of cholestasis such as itching. He led an active life and worked as a hiphop journalist. At the age of 21 he showed progressive jaundice. Endoscopic retrograde cholangiopancreatography (ERCP) revealed stenosis of the bile duct. A balloon dilatation of the common bile duct with stenting was performed, resulting in a decrease in the bilirubin levels to pre-existing values. The same year the stent was removed without any effect on the cholestasis. Also, he was diagnosed with pT3N1bM0 papillary thyroid carcinoma at the age of 23, for which he was curatively treated with a total thyroidectomy plus lymph node dissection and radioactive iodine therapy.

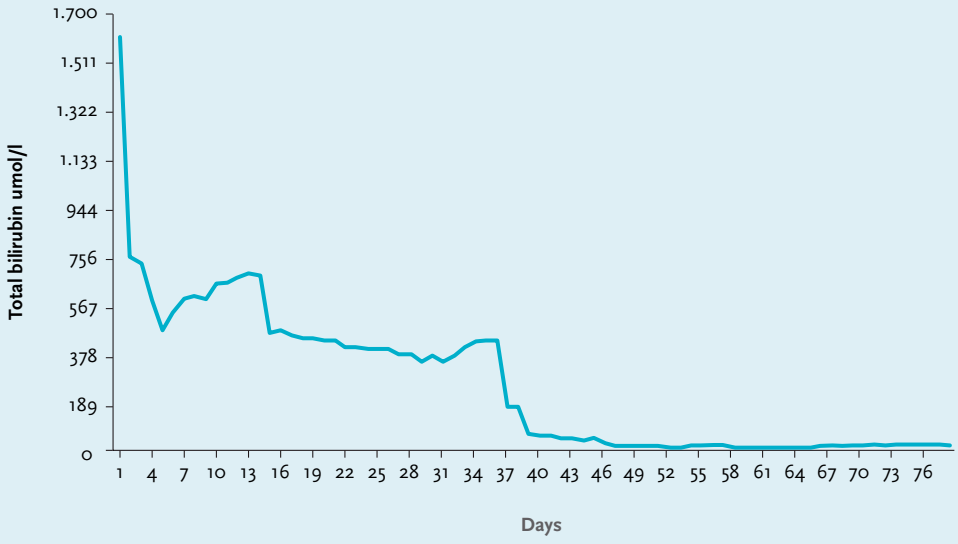
Two weeks before admission to our ICU, he presented himself in another hospital with complaints of fatigue and

progressive jaundice. These symptoms had slowly progressed over the months before. ERCP and sonography showed no signs of bile duct obstruction. Revision of the liver biopsy performed in 2012 showed intrahepatic cholestasis with some portal and parenchyma fibrosis, without iron or copper overload. During his admission, he developed coagulopathy and visual disturbances and a few days later also renal failure. Because there was a suspicion of acute hepatic failure with hepato-renal syndrome requiring a liver transplant, he was transferred to our ICU.

On admission, his total bilirubin level was 1613 µmol/l and almost entirely conjugated, haemoglobin was 4.6 mmol/l, his activated partial thromboplastin time (APTT) was 124 seconds and his creatinine level was 638 µmol/l (*table 1*). Encephalopathy grade 2 was present.[5] Autoimmune and viral serology revealed no aetiology for his clinical deterioration. A sonography of liver and heart showed no major abnormalities. The diagnosis fulminant hepatic failure of unknown origin was made. On admission he already met the Kings College criteria for acute liver transplantation and he was placed on the transplantation waiting list.[5,6] To bridge time to transplantation, molecular adsorbent recirculation system (MARS) therapy combined with continuous veno-venous haemofiltration (CVVH) was started. This quickly improved his liver and renal function and the patient also improved clinically. His neurological symptoms disappeared. The request for a donor liver was put on hold temporarily, because of his improved liver synthesis as measured by coagulation parameters. After four days he could be discharged to the ward, at which time his total bilirubin levels were 516 µmol/l and his coagulation tests were normal.

After six days the patient was readmitted to the ICU because he had a fever, pain on his left flank and hypotension. Also, his bilirubin levels were increasing again and he developed extreme pain in his right upper quadrant. A liver biopsy showed massive intrahepatic cholestasis with porto-septal fibrosis but also peri-sinusoidal and centrilobular fibrosis, without signs of a primary and/or obstructive biliary disease. Three days later he developed progressive hypotension and bradycardia. Echocardiography now showed a large pericardial effusion, causing a tamponade. A pericardiocentesis was performed and haemorrhagic fluid was drained. There was improvement for a few hours but then again he developed hypotension followed by cardiac arrest. An emergency thoracotomy was performed in the ICU, which resulted in a return of spontaneous circulation after removal of blood and clots from the pericardium. Three days later, he again developed a tamponade and a re-thoracotomy was performed in the operating room. No micro-organisms were cultured from the pericardial fluid. For the entire period in the ICU, his haemoglobin levels were kept > 9 mmol/l to suppress erythropoiesis and subsequent haemolysis. CVVH was continued for renal failure. Bilirubin levels remained around 400 µmol/l. Magnetic resonance cholangio-pancreatography to exclude bile duct obstruction again showed no abnormalities. Four days after the last thoracotomy the request for a donor liver on the high urgency list was reactivated. Eleven days later he underwent a liver transplantation and received a full-size liver from a heart beating donor. Two days after that a re-laparotomy was performed

Figure 1. *Bilirubin levels during hospital admission. On day 1 the patient received MARS + CVVH therapy. On day 36, liver transplantation was performed*



because of intra-abdominal haemorrhage. Shortly hereafter the patient stabilised: his total bilirubin level dropped directly postoperatively to 162 µmol/l and ten days later it was 26 µmol/l (*figure 1*). CVVH could be discontinued because of the return of spontaneous diuresis. Intermittent haemodialysis was started. One week after liver transplantation he was discharged to the ward. The histology of the explanted liver showed massive cholestasis with bile thrombi in dilated canaliculi, in ductular and ductal lumina and bile sludge in the larger ducts without features of cholangitis. There were numerous foci of groups of hepatocytes with feathery degeneration, a feature of hepatocyte loss due to severe cholestasis. The liver showed diffuse septal fibrosis with porto-portal and porto-central bridging and also sinusoidal fibrosis. Months later genotyping revealed that the patient had Gilbert's syndrome as a second SNP. Meanwhile, the patient was doing well and he could perform his job again. His bilirubin levels stayed within normal limits.

Figure 2. *Fibrotic portal tract with ductular reaction. Bile thrombi are present in ductular lumina (arrows). The centrally located bile duct (asterisk) does not show cholangitis and bile thrombus. (Masson thrichrome staining, 20x objective)*

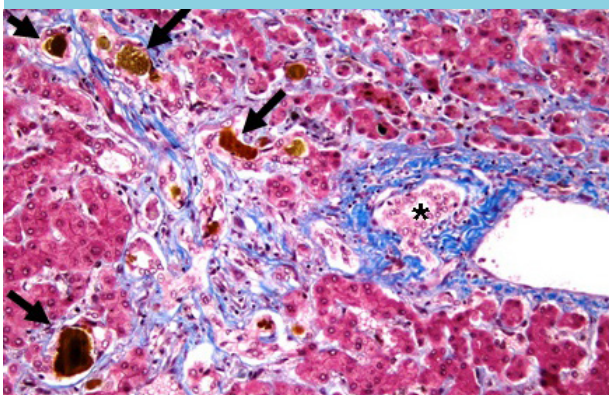
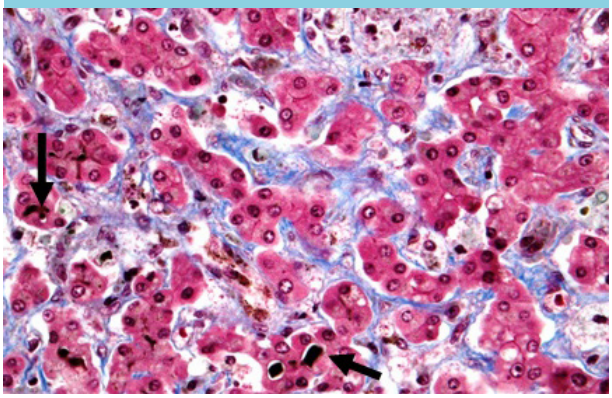


Figure 3. *Bile thrombi in dilated canaliculi (arrows) and sinusoidal fibrosis as shown by collagen (blue strands) deposition in the sinusoids. (Masson thrichrome staining, 40x objective)*



DISCUSSION

This patient was transferred to our hospital with the clinical diagnosis of fulminant hepatic failure of unknown origin, but probably related to his rare haematological condition. This disease is called Mizuho after the Japanese residence were the first patient was described. Very little is known about this disease because there are only four cases reported in the literature, all without long-term follow-up; one describes our patient.[1-4] After splenectomy this disease seems to have a relatively benign course.[1-4] In this patient there was no severe haemolysis as measured by lactate dehydrogenase. MARS was started as a bridge to transplantation.[7] After that, the bilirubin levels halved and the patient improved considerably. Encephalopathy and coagulation disorders disappeared and the synthesis function of the liver appeared normal. Liver transplantation was postponed to await further improvement. But then, rising bilirubin levels and pericardial tamponade urged further therapy. He was again placed on the transplantation list under the diagnosis of chronic haemolysis with unknown underlying hepatic disease leading to bilirubin toxicity. Liver damage due to chronic cholestasis, both hepatocellular and in intra- and extra-hepatic bile ducts, was considered an alternative. However, liver biopsy did not reveal a specific diagnosis. Genetic tests were ordered but the results were still pending at the moment of transplantation.

Our hypothesis was based on the literature. The main issue and ultimately the clue was that this patient with a relatively low-grade haemolysis showed this level of jaundice with most of the bilirubin conjugated. This conjunction of laboratory findings could not be fitted in a single known syndrome as fulminant hepatic failure, bile duct obstruction, haemolysis or any other. There are several inherited diseases with chronic or intermittent haemolysis with a higher incidence than Mizuho. These diseases have a widely differing geographical distribution but are far more common than Mizuho.

Sickle cell disease (SCD) and thalassaemia are also haemoglobinopathies. Furthermore, glucose-6-phosphate dehydrogenase (G-6-PD) and spherocytosis are metabolic disorders of the erythrocyte that lead to haemolysis.

Sickle cell anaemia and thalassaemia can lead to liver failure.[8,9] SCD is associated with hepatopathy.[10] Liver failure in SCD is, next to complications of sickling, due to transfusion-related infections and iron overload.[11-14] Sickle cell intrahepatic cholestasis (SCIC) is an extremely rare complication of SCD.[15] The clinical presentation of SCIC includes severe abdominal pain, acute hepatomegaly, coagulopathy, extreme hyperbilirubinaemia and acute

hepatic failure, which can also lead to renal failure. For adults this is a potentially fatal process.[13,16-18] In children it sometimes resolves spontaneously.[19] The cause of SCIC is unknown but in the literature the presumed pathogenesis is that sickling red blood cells plug the hepatic sinusoids causing cholestasis and local hypoxia.[12,13,16] Hyperbilirubinaemia is mainly conjugated in contrast to hyperbilirubinaemia due to haemolysis which is mostly unconjugated.[13] Treatment consists of supportive care and prompt exchange transfusion to minimise haemolysis.[10,13,16] However, this may not always lead to improvement. There are a few case reports of patients with SCIC who received liver transplantation. One recent article by Gardner *et al.* describes a patient with suspected SCIC in a chronic form, developing hepatic failure ten years later.[13] The patient responded very well to liver transplantation and two years later he was still in a good condition. Most patients improve after exchange transfusion which not only removes sickling cells, but also a substantial amount of albumin-bound bilirubin.[15,16] Except for the fact that our patient did not suffer from SCD, his clinical presentation strongly resembles SCIC. Moreover, the case of Khurshid et al. is the first one to also develop a tamponade with haemorrhagic fluid in the pericardium and later on brady-arrhythmias.[15] The pericardial bleeding was probably caused by coagulopathy combined with heparin administration through CVVH. Extreme hyperbilirubinaemia is associated with renal failure and coagulopathy.[17] Our patient has the extremely high levels of bilirubin in common, which may be a leading factor in disease development. Unlike in our patient, SCD causes chronic haemolysis with bouts during crises leading to high bilirubin.

The most robust genetic association that modifies the clinical phenotype of haemoglobinopathies is Gilbert's syndrome; however, several others have been described.[20-22] Beta thalassemia intermedia or major and sickle cell anaemia can co-occur with Gilbert's syndrome and lead to increased bilirubin.[23] Gilbert's syndrome was described for the first time in 1901.[24] The incidence of Gilbert's syndrome in the general population is approximately 8%.[25-27] There is racial variability.[26,28-30] Gilbert's syndrome is caused by a genetic defect in bilirubin conjugation with glucuronide. Mutations in the promoter region of UGT1A1 are the most frequent polymorphism.[31] UGT1A1 promoter with 7 TA repeats in the promoter region has less enzyme activity than the most frequent genotype with 6 repeats.[28] An increasing number of repeats decreases the transcription efficiency 20-fold.[29,31] Our patient had 7 repeats. The diagnosis of Gilbert's syndrome is usually based on unconjugated hyperbilirubinaemia without haemolysis, normal liver tests and normal ultrasonography of the liver.[25,32] This makes the diagnosis complicated in patients with chronic haemolysis as in haemoglobinopathies.[33] UGT1A1 (TA)7 is associated with higher bilirubin, cholelithiasis and cholecystectomy in SCD, β-thalasaemia, hereditary spherocytosis and G-6-PD.[30,34-40] Our patient had gallstones and a cholecystectomy at the age of 4, which could have triggered the suspicion of a concomitant disorder if the similarity with other haemoglobinopathies had been recognised. As a child our patient suffered from hyperbilirubinaemia which was mainly unconjugated, as could be expected in both haemolysis and Gilbert's syndrome. In this episode his hyperbilirubinaemia was mainly conjugated as has been described in SCIC with extremely high bilirubin.[13] The explanation for this shift is hypothetical but it might be chronic toxicity of extremely high bilirubin.

For acute SCIC prompt exchange transfusion is the therapy of choice. But in extreme hyperbilirubinaemia MARS might have an important additional beneficial effect as shown in this patient. However, MARS clears the plasma compartment only. Our patient was deep dark green reflecting the loading of tissues with bilirubin, and this might explain the early relapse in our patient. Plasmapheresis in extreme hyperbilirubinaemia is also probably effective by removing albumin-bound bilirubin.[15,41,42] Using the same strategy, looking for analogies we did not find an explanation for the thyroid carcinoma. Thus far we consider it to be a coincidence.

CONCLUSION

Molecular diagnostics revealed a very rare disease for this patient in his childhood. The unfamiliarity with this disease initially leads to the attribution of all symptoms to Mizuho's disease. However, molecular diagnostics also made it possible to diagnose Gilbert's syndrome, which is normally diagnosed on clinical grounds if there is no haemolysis. As with other rare and complicated diseases not all symptoms and his complete history can be explained. But this history illustrates that the phenotype of a genetic syndrome heavily depends on the rest of the genotype. It is important to always look for other causes if symptoms cannot be explained with the disease a patient is already diagnosed with. It also illustrates that in rare diseases the clue can sometimes be found searching in the immense available literature for analogy. In this patient liver transplantation could fortunately repair one of his diseasing polymorphisms.

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DISCLOSURES

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PHOTO QUIZ

An elderly man with swelling and discolouration of the right earlobe

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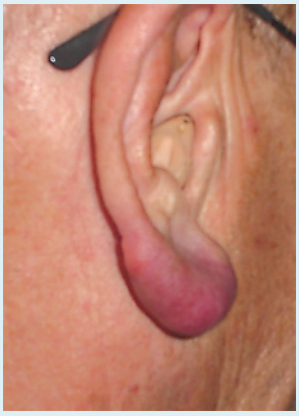
CASE REPORT

In 2006, an 83-year-old Caucasian male presented himself to the outpatient clinic with cosmetic complaints of an increasingly purple-coloured right earlobe, which had developed over the last few months. His medical history consisted of hearing loss on both sides since 1993, without a clear ENT focus. Intoxication showed no smoking and moderate alcohol consumption (2 units/day). The patient was not on regular medication and had no allergies. The swelling was not painful and he had no weight loss, fever or night sweats. He otherwise felt well and had no other complaints. Upon physical examination it was found that the swelling was purple-red, non-tender and that it felt rubbery. There were no palpable lymph nodes and no hepatosplenomegaly. The neurological exam was unremarkable. A biopsy was performed in the surgery department.

Figure 1a. *Swelling and discolouration of the earlobe*



WHAT IS YOUR DIAGNOSIS?

See page 256 for the answer to this photo quiz.

PHOTO QUIZ

An abnormal serum protein electrophoresis

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CASE REPORT

A 29-year-old woman, with a medical history of vitamin D deficiency as well as an iron deficiency due to hypermenorrhoea, presented to our outpatient clinic with fatigue and an elevated erythrocyte sedimentation rate (ESR). She was referred by the family doctor to exclude an underlying disease. Besides feeling tired, which had existed for years and was normally aggravated during winter, she had no other symptoms. Physical examination was unremarkable. Laboratory investigations showed: C-reactive protein 3 mg/l (0-10), leucocytes 7.7 10^9/l (4.3-10.0), ESR 33 mm/h (0-20), vitamin D 18.5 nmol/l (> 50), total protein 64 g/l (60-80), albumin 37.3 g/l (36.8-45.9). Serum protein electrophoresis was performed (*figure 1A and table 1*). Chest X-ray and an abdominal ultrasound were normal.

WHAT IS YOUR DIAGNOSIS?

See page 258 for the answer to this photo quiz.

Table 1. *Serum protein electrophoresis fractions*

Fractions	%	g/l	Ref. g/l
Albumin	58.3	37.3	40.2-47.6
Alpha 1	4.2	2.7	2.1-3.5
Alpha 2	9.5	6.1	5.1-8.5
Beta	10.6	6.8	6.0-9.4
Gamma	17.4	11.1	8.0-13.5

Figure 1A. *Serum protein electrophoresis performed on our patient*

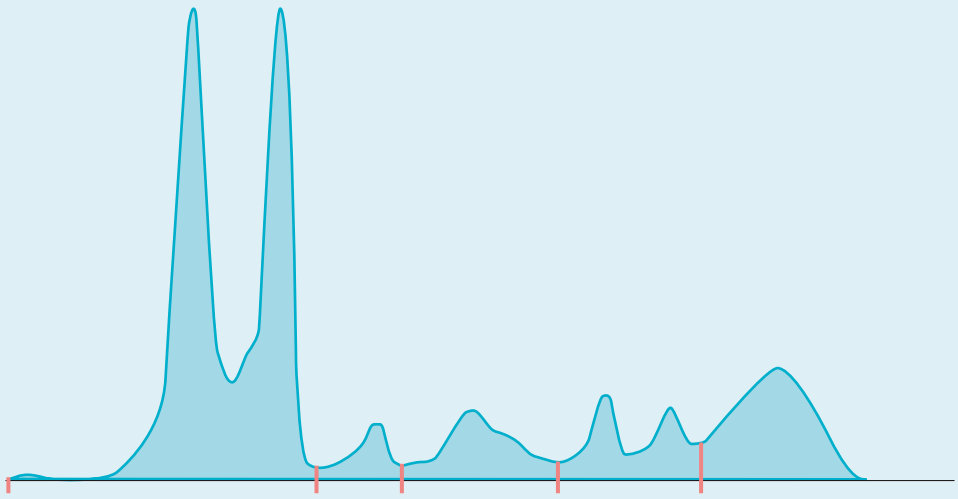

PHOTO QUIZ

A young man with vision loss: keep your eyes open for a rare cause

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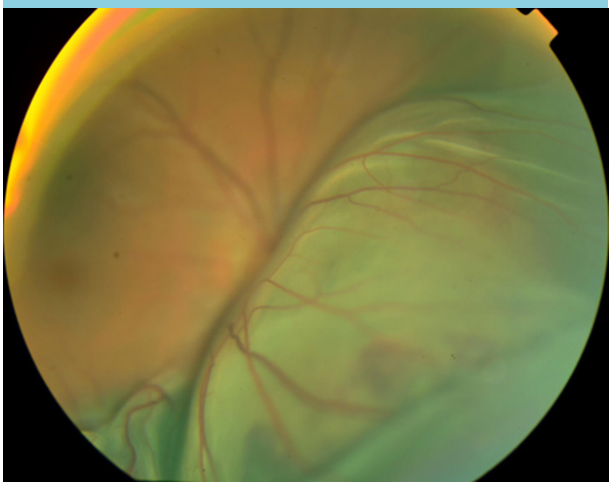
CASE REPORT

A 19-year-old Caucasian male with no previous medical history, presented to our outpatient clinic with a one-week history of pain, redness and decreased visual acuity (1/60) of the right eye. Fundoscopy showed a large subretinal lesion with subretinal fluid accumulation (*figure 1*). On further physical examination an elastic swelling with a diameter of 10 mm was found on his back. He had also had an enlarged right testicle for as long as he could remember, and he had not noticed a difference in the last five years. Initial laboratory investigations showed a slightly elevated lactate dehydrogenase (282 IU/l). B-scan ultrasonography of the eye revealed an irregular, medium-high reflective choroidal tumour with a diameter of 20 mm and a thickness of at least 12 mm.

Computed tomography of chest and abdomen showed multiple intra-pulmonary lesions, suspected for metastases. Magnetic resonance imaging of the brain showed an intraocular mass of the right eye with haemorrhage (*figure 2*) and an intracerebral lesion.

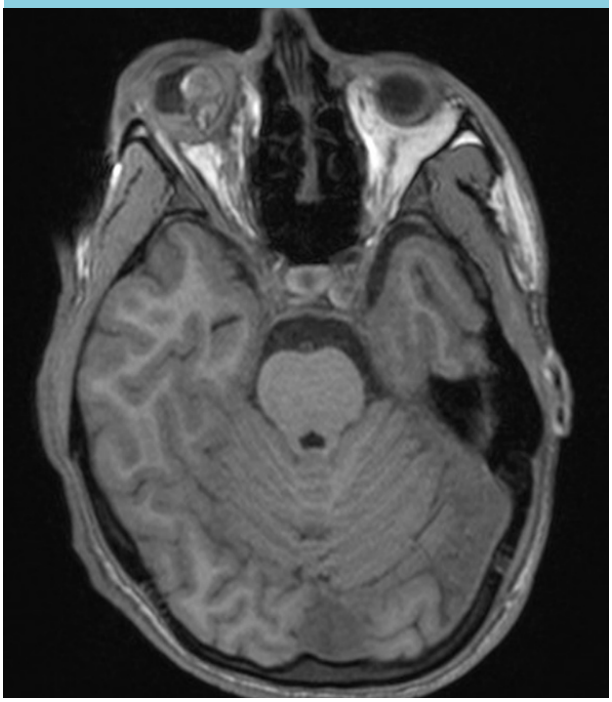
Figure 1. *Fundoscopy, a large subretinal lesion with subretinal fluid accumulation and retinal detachment*



WHAT IS YOUR DIAGNOSIS?

See page 259 for the answer to this photo quiz.

Figure 2. *Head MRI (T1-sequence), an intraocular mass of the right eye with probable haemorrhage*



ANSWER TO PHOTO QUIZ (PAGE 253)

AN ELDERLY MAN WITH SWELLING AND DISCOLOURATION OF THE RIGHT EARLOBE

DIAGNOSIS

The pathology report showed a B-cell chronic lymphocytic leukaemia (B-CLL) with cutaneous involvement. No B-symptoms and no lymphadenopathy were present. Laboratory investigation of peripheral blood showed neither anaemia nor thrombocytopenia, but it did show a leukocytosis of 36.6 x 10*9 cells/l, with a differential count of 82% lymphocytes. The lactate dehydrogenase was not elevated and the soluble immunoglobulins G and M were decreased (IgG: 3.9 g/l; IgA: 1.5g/l; IgM: < 0.30g/l). Chest radiography and ultrasound of the abdomen showed an enlarged spleen (15 cm) but no other localisations of the lymphoma, which depicts a RAI stage II. The immunophenotype of the peripheral blood showed a monoclonal B-cell population IgM/IgD lambda (84%) and these B-cells were CD5+CD19+CD20+CD23+CD38+FMC7-, consistent with a B-CLL. Immunohistochemistry of the biopsy showed CD20 positive atypical lymphocytes with no relation with the epidermis (*table 1 and figure 2*).

There was no indication for treatment based on the International Workshop on CLL/ National Cancer Institute working group (IWCLL/NCI) criteria.[1] Because the earlobe was progressively swelling, however, the choice was made to start systemic therapy with chlorambucil 4 mg once daily for two weeks. As the earlobe did not respond to this treatment, the dose of chlorambucil was subsequently increased to 10 mg once daily for intervals of two weeks every month for four months. The leukaemia of the earlobe appeared refractory to this treatment, nevertheless the lymphocytosis decreased. Consequently the earlobe was irradiated, first with 4.0 Gy, with partial effect, and later with six doses of 2.5 Gy, with complete remission (*figure 1b*). Since then his clinical stage is a Binet stadium A and has been stable without any further treatment for the last seven years.

Figure 1b. *The earlobe after irradiation in complete remission*

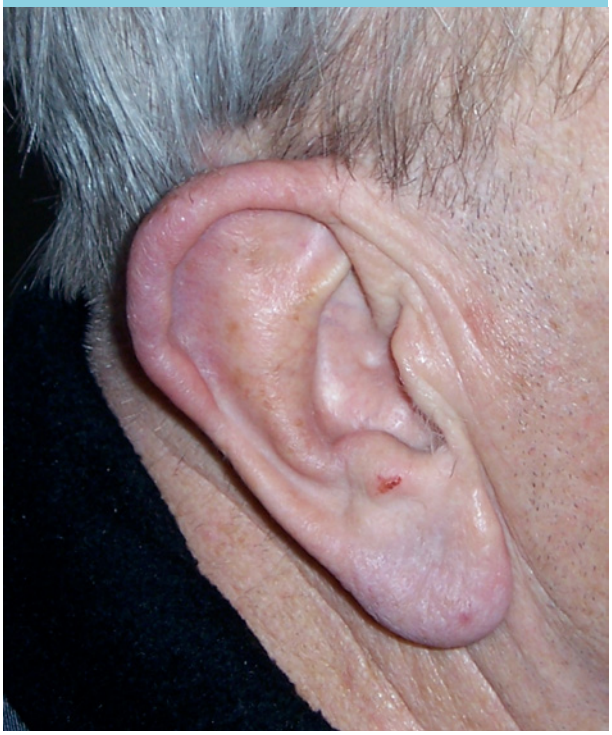


Figure 2. *Pathology of the biopsy of the cutaneous lesion a. Atypical lymphocytes (HE staining 400x) b. All atypical lymphocytes show CD20 positivity (CD20 staining 400x)*

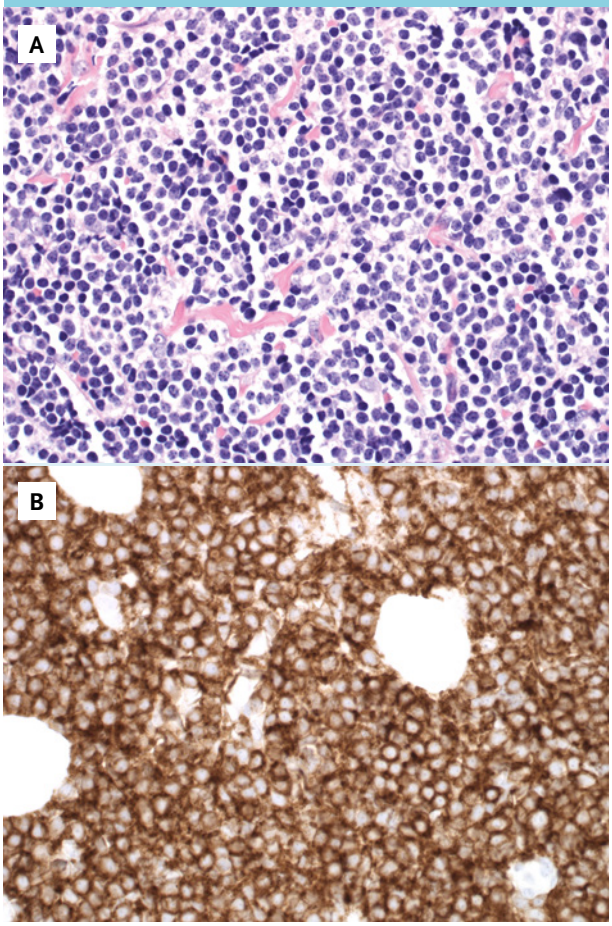


Table 1. *Immunohistochemistry of the biopsy*

	Positive	Negative
B-cell markers	CD20	CD10
	CD23	BCL-6
	CD79a	
	BCL-2	
T-cell markers	CD3	
	CD5	
	CD45RO	

Cutaneous involvement of a B-CLL has not been widely described. There is one article describing 42 patients with cutaneous involvement of a B-CLL,[2] in which duration of B-CLL before skin manifestations varied from zero to 142 months and in our patient this was approximately 48 months. In seven of the 42 patients the cutaneous lesion was the first sign of the disease. The lesions were confined to the head, neck, trunk or extremities and no earlobe lesions were described. In another article, histological variables that independently correlated with relatively short survival included an infiltrate of severe intensity, a diffuse pattern, epidermal changes (especially acanthosis and ulceration), medium-sized and large B-lymphocyte (more than 5%), and reactive cells within the infiltrate (neutrophils, eosinophils, and plasma cells).[3] None of these criteria applied to our patient; although there is infiltration with reactive T-cells. The patients in the group with no histological variables that correlated with shorter survival had an estimated five-year survival of 66.6%.

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ANSWER TO PHOTO QUIZ (PAGE 254)

AN ABNORMAL SERUM PROTEIN ELECTROPHORESIS

DIAGNOSIS

Serum electrophoresis performed on our patient showed a rarely encountered serum protein anomaly, where not one but two distinct albumin bands were found (*figure 1B*). This phenomenon is known as bisalbuminaemia or alloalbuminaemia and is the concurrence of having two kinds of serum albumin that differ in mobility on electrophoresis. It was first described in 1955 by *Scheurlen* in a diabetic German. It occurs in a hereditary and in an acquired form.[1] The acquired (or transient) form of bisalbuminaemia has been described in patients receiving high doses of B-lactamic antibiotics or suffering from pancreatic disease. Hereditary (or permanent) bisalbuminaemia is usually revealed by chance, as it is a relatively rare genetic disorder.[2] Several families worldwide have been identified as suffering from hereditary bisalbuminaemia. A variety of polymorphisms and mutations have been reported in the literature in the last decades. Today, 77 mutations of the albumin gene are known, with 65 of them resulting in bisalbuminaemia.[3]

Bisalbuminaemia causes no symptoms and has most commonly been reported as a benign condition, found as a concomitant phenomenon.[4] It is therefore unlikely that the symptoms in our patient are explained by this bisalbuminaemia. We were unable to perform serum protein electrophoresis on our patient's family. There are no guidelines or recommendations available regarding follow-up, its clinical significance is uncertain.

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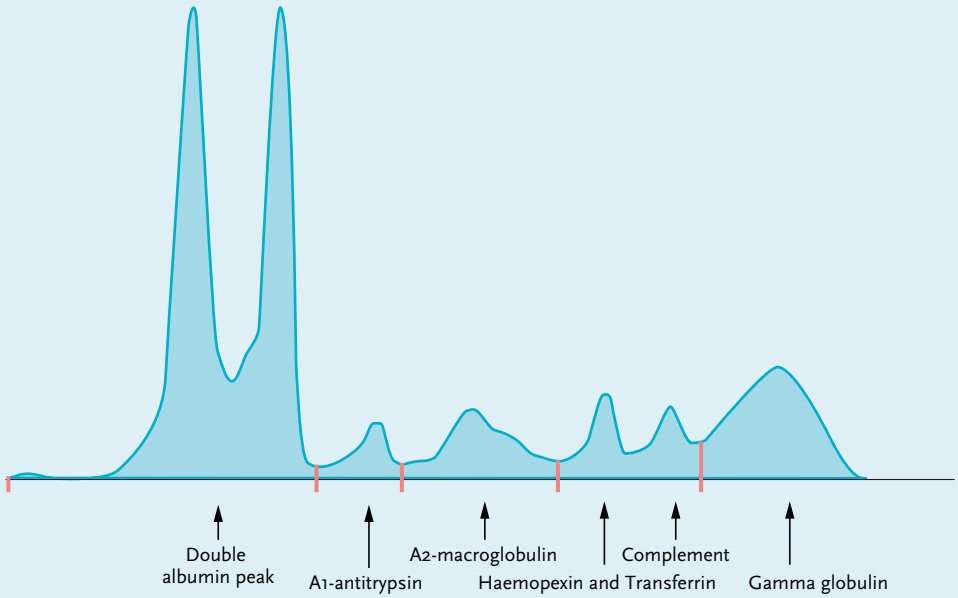
Figure 1B. *Serum protein electrophoresis*



ANSWER TO PHOTO QUIZ (PAGE 255)

A YOUNG MAN WITH VISION LOSS: KEEP YOUR EYES OPEN FOR A RARE CAUSE

DIAGNOSIS

Fundoscopy and radiological findings showed a large yellow subretinal tumour with haemorrhage, subretinal fluid accumulation and retinal detachment. The differential diagnosis included a choroidal metastasis and a primary metastatic choroidal melanoma. Choroidal metastases are the most common form of uveal metastases and on fundoscopy they are usually yellow in colour and associated with subretinal fluid.[1] On a B-scan ultrasonography, choroidal metastases typically have an irregular contour with a medium-to-high reflectivity, while choroidal melanomas have a smooth, dome shape with low-to-medium reflectivity. Therefore a choroidal metastasis was more probable than a choroidal melanoma. Besides choroidal melanomas with pulmonary metastases without liver metastases are highly unusual.

A cytological biopsy of the subcutaneous mass on his back showed a metastatic choriocarcinoma. Additional laboratory testing revealed an α-fetoprotein of 210 μg/l (reference range < 10 μg/l) and a beta-human chorionic gonadotropin of 3900 ng/ml (reference range < 1 ng/ml). The diagnosis stage IVB nonseminomatous germ cell tumour (poor risk) was made. We started first-line chemotherapy (etoposide, cisplatin and bleomycin), followed by an orchidectomy. Pathology showed a necrotic tumour with mature teratoma as the only vital part.

Metastatic cancer is believed to be the most common form of intraocular malignancy in adults. The proportion of patients with intraocular metastasis among 716 unselected patients with cancer at the time of death was estimated to be 4%.[2] Symptoms can be (sub)acute vision loss, scotoma, pain, swelling and redness of the eye. Breast cancer is the most common primary tumour, followed by lung cancer and gastrointestinal cancer.[1,2] Choriocarcinoma, however, is a rare cause of choroidal metastases. Unlike other metastatic ocular disease, significant haemorrhage is associated with choriocarcinoma metastases. This may be correlated with upregulation of vascular endothelial growth factor.[3]

Prognosis and treatment of choriocarcinoma patients with choroidal metastases are not clear, while most literature is from before the introduction of platinum-based chemotherapy and only consists of case reports.[3] The treatment spectrum in these case reports covers chemotherapy only, chemotherapy in combination with whole brain radiotherapy (WBRT), or chemotherapy in combination with WBRT and (stereotactic) radiotherapy of the eye.[4]

Metastatic choriocarcinoma should be considered in patients with choroidal tumours, especially in case of significant haemorrhage of the tumour and a young age at presentation. Therefore, testicular examination should not be forgotten in these cases.

CONSENT

Written informed consent was obtained from the patient for publication of this Case Report. A copy of the written consent is available for review by the Editor of this journal.

ACKNOWLEDGEMENTS

The authors would like to extend their gratitude to Ann-Laure Delbecq and Dorus Kouwenberg. None of the authors have a conflict of interest to declare.

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INFORMATION FOR AUTHORS

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2. Kaplan NM. Clinical Hypertension. 7th ed. Baltimore: Williams & Wilkins; 1998.
3. Powell LW, Isselbacher KJ. Hemochromatosis. In: Braunwald E, Fauci AS, Kasper DL, et al., editors. Harrison's Principles of Internal Medicine. 15th edition. New York: McGraw-Hill; 2001. p. 2257-61.

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Case reports containing concise reports on original work will be considered for publication. Case reports which are relevant for understanding the pathophysiology or clinical presentation of disease may also be accepted under this heading. Selection of case reports will be based on criteria as outlined in a special report by the editors (Drenth et al. The case for case reports in *the Netherlands Journal of Medicine*. Neth J Med. 2006;64(7):262-4). We advise potential authors to take notice of the instructions in this report. Articles published in this section should be no longer than 1000 words, and supplied with a summary of about 60 words, preferably no more than two figures and/or tables, and no more than 15 references. In addition, we require that authors of case reports answer the following two questions (Neth J Med. 2008;66(7):289-90): 1) What was known on this topic? and 2) What does this add? The answers will appear in a separate box in the text.

Mini reviews

Mini reviews are concise notes that bring the reader up to date with the recent developments in the field under discussion. The review article should mention any previous important reviews in the field and contain a comprehensive discussion starting with the general background of the field. It should then go on to discuss the salient features of recent developments. The authors should avoid presenting material which has already been published in a previous review. The manuscript should be divided as follows: title page, abstract and main text. The text may be subdivided further according to the areas to be discussed. The text should not exceed 2500 words.

Letters to the editor (correspondence)

Letters to the editor will be considered by the editorial board. Letters should be no more than 400 words. Please use SI units for measurements and provide the references conform the Vancouver style (N Engl J Med. 1991;324:424-8). No more than one figure is allowed. For letters referring to articles previously published in the Journal, the referred article should be quoted in the list of references.

Photo quiz

A photo quiz should not exceed 500 words and include no more than two figures and four references conform the Vancouver style. Abbreviations of measurements should be quoted in SI units.

Book reviews

The editorial board will consider articles reviewing books.

Reviewing process

After external and editorial review of the manuscript the authors will be informed about acceptance, rejection or revision. We require revision as stated in our letter.

Proofs

Proofs will be sent to the authors to be carefully checked for printer's errors. Changes or additions to the edited manuscript cannot be allowed at this stage. Corrected proofs should be returned to the editorial office within two days of receipt.

Offprints

These are not available. The first author receives a sample copy of the Journal with the published article.