Light blue sclerae and normal bones: what is your diagnosis?

Extracranial giant cell arteritis

Maturity onset diabetes of the young

Eligibility criteria of Dutch dementia research protocols

Intravenous lipid emulsion in hydroxychloroquine intoxication
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LETTER
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Giant cell arteritis (GCA) was first described as a temporal arteritis by Horton, Magath and Brown in 1932, but Cooke et al. already demonstrated in 1945 by autopsy that it could be a generalised vasculitis of the aorta and its main branches. In fact, Cooke recognised that in the elderly ‘a widespread arterial disease existed, not uncommon but rarely recognised’. Moreover he stated that the term temporal arteritis has been retained to indicate a specific clinical entity in the absence of any definite aetiological factor. Nowadays, with the availability of modern age imaging (ultrasound, PET-CT, CTA, MRA,) the awareness of extracranial GCA has risen significantly. GCA is the most prevalent form of systemic vasculitis, especially in ageing Caucasian populations.

Lensen et al. wrote an elaborate narrative review on extracranial GCA. It is apparent that a clear consensus on the best diagnostic imaging modality is lacking and that the diagnosis is usually based on the clinical signs and symptoms together with the locally available imaging modalities and expertise. Also, they point out that evidence-based treatment guidelines are lacking and that the same treatment regimen for cranial and non-cranial GCA is applied. Moreover, it is unclear what the best strategy is to monitor disease activity and how to deal with relapsing patients. The latter is a clear problem since up to 64% of patients with GCA experience a relapse. Part of the lack of knowledge and/or consensus might be due to the high variability in presenting clinical symptoms, from headache to night sweats and polymyalgia rheumatica like symptoms, as well as the associated dispersion over many different medical specialists, including general practitioners, neurologists, ophthalmologists, internists, rheumatologists, and vascular surgeons. It is increasingly recognised that GCA is a debilitating disease, which causes significant morbidity in otherwise healthy 50+ persons, not in the least due to the long-term use of glucocorticoids.

Improving outcome has to start with early and timely recognition of patients presenting with GCA. Especially cranial GCA symptoms are linked to irreversible loss of vision and this could be prevented by early aggressive treatment with steroids. Also, the recognition of aortic structural damage including aneurysm development is of importance. However, long-term incidence and the relative contribution of atherosclerotic and inflammatory components are unclear and better studies are needed.

Fast-track clinical pathways have been established in several specialist centres, providing initial diagnostic evaluation and treatment of patients with suspected GCA within 24 hours. Preliminary results suggest a significant reduction of permanent visual impairment compared with conventional referral strategies. Another important issue that needs to be addressed is increasing public and general practitioner awareness of GCA as a debilitating disease in order to reduce the referral time to the fast track clinic.

Ideally a fixed work-up protocol with standardised and validated lab and imaging techniques should be available in a day-care setting. In such a setup, ultrasound is a promising tool, and not only for cranial GCA, as it is easily accessible and relatively inexpensive in contrast to more advanced imaging strategies. Since the landmark study by Schmidt in 1997, several studies on the use of Duplex ultrasound (combination of colour Doppler and pulsed-wave-Doppler) in the diagnosis and follow-up of cranial GCA have been published. In addition to early detection of stenosis and occlusion, a typical dark hypoechoic, circumferential wall thickening is usually observed in a vessel affected by vasculitis, referred to as the ‘halo’ sign. For cranial GCA, the accuracy has been tested in several studies, using histological diagnosis as the gold standard, yielding good sensitivity, specificity, and reproducibility when performed by
experienced sonographers. Preliminary results from the recently completed prospective multicentre TABUL study (Temporal Artery Biopsy vs Ultrasound in diagnosis of GCA; NCT00974883) including 415 cases with suspected cranial GCA suggests that ultrasound is only of diagnostic value if performed within four days of steroid initiation as the typical halo quickly diminished over time. Of importance, these typical ultrasound signs can also be observed in patients with extracranial GCA, predominantly affecting axillary, subclavian and/or proximal brachial arteries. Clinical cohorts have suggested that the axillary artery may be very useful and is generally found to be affected in most cases of extracranial GCA. However, contrary to temporal ultrasound, it is not possible to use histology as a gold standard and no formal validation study has been performed.

Treatment should be started promptly in GCA patients with cranial symptoms, but can probably be delayed in extracranial GCA in order to make the proper diagnosis. Whether aggressive treatment also leads to a decrease in long-term aortic structural damage is as yet unclear. Imaging studies clearly show that the inflammatory signal rapidly decreases after starting glucocorticoids. Treatment is still based largely on glucocorticoids monotherapy, but the disease-modifying antirheumatic drugs methotrexate, lefunomide, azathioprine and a very recently published randomised controlled trial (RCT) in 30 patients with tocilizumab, an IL6-receptor blocking biological, have demonstrated varying benefits. The results of the much larger international four arm double-blinded RCT with tocilizumab and different steroid-tapering regimens (GiACTA, NCT01791153) are awaited soon.

In summary, Lensen et al. highlight a number of challenges in extracranial GCA and new developments give us hope that it will not take another 70 years to solve the areas of uncertainty presented in their discussion.

REFERENCES

Extracranial giant cell arteritis: A narrative review

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ABSTRACT

A systematic literature search was performed to summarise current knowledge on extracranial giant cell arteritis (GCA), i.e. large-artery involvement in patients with or without clinically apparent temporal arteritis (cranial GCA). Extracranial GCA is increasingly recognised, both in patients with cranial GCA and with solitary extracranial GCA, due to increased awareness among physicians and development of modern imaging modalities. The literature on the pathogenesis and histopathology of extracranial GCA is scarce. It is considered to be similar to cranial GCA. Patients with solitary extracranial GCA often present with non-specific signs and symptoms, although vascular manifestations, mostly secondary to stenosis, may occur. Due to the non-specific clinical presentation and low sensitivity of temporal artery biopsies, extracranial GCA is usually diagnosed by imaging. ¹⁸F-FDG-PET, MRI, CT angiography and ultrasound are used for this purpose. At present, the optimal diagnostic strategy is undetermined. The choice for a particular modality can be guided by the clinical scenario that raises suspicion of extracranial GCA, in addition to local availability and expertise. Extracranial complications in GCA consist of aortic aneurysm or dissection (mainly the ascending aorta), aortic arch syndrome, arm claudication and posterior stroke (although this is technically a cranial complication, it often results from stenosis of the vertebrobasilar arteries). Mortality is generally not increased in patients with GCA. Treatment of patients with solitary extracranial and those with extracranial and cranial GCA has been debated in the recent literature. In general, the same strategy is applied as in patients with temporal arteritis, although criteria regarding who to treat are unclear. Surgical procedures may be indicated, in which case optimal medical treatment prior to surgery is important.

KEYWORDS

Giant cell arteritis, vasculitis, arteritis, extracranial

INTRODUCTION

Giant cell arteritis (GCA) is a granulomatous vasculitis of unknown origin, affecting large and medium-sized arteries. Temporal arteritis is a well-known clinical phenotype of GCA, characterised by temporal headache, jaw claudication and visual symptoms and is sometimes referred to as cranial GCA. In fact, large-artery involvement, mainly aortic, subclavian and vertebral artery, appears to be common in patients with cranial GCA. In addition, recent studies have suggested that GCA quite often manifests exclusively in large arteries, i.e. the aorta and proximal branches, with specific signs or symptoms frequently not present. This has been referred to as ‘silent’ or ‘extracranial’ GCA. Diagnostic delay in extracranial GCA, i.e. without cranial manifestations, is a potential source of disease burden and complications. The goal of this review is to summarise the current knowledge on large-artery involvement in GCA which, for the purpose of this review, is further referred to as extracranial GCA.

METHODS

A systematic literature search was performed to collect articles on extracranial GCA (figure 1). For the purpose of this review, and in view of the lack of well-defined terminology for extracranial GCA in the current medical literature, three separate groups were defined prior to the selection of relevant articles, namely:
1. **Solitary cranial GCA**: patients fulfilling the following:
A) 1990 American College of Rheumatology criteria for GCA
B) Histological proof of temporal arteritis
C) Clinical impression of temporal arteritis (assessed by physician based on typical features, e.g. scalp tenderness, jaw and tongue claudication) all of which lack evidence of large-artery involvement (either clinically or excluded by imaging).

2. **Cranial GCA with established extracranial involvement**: (i.e. aorta, subclavian, vertebral, carotid, axillary, iliac and femoral artery), which was confirmed by:
A) A typical combination of signs/symptoms, laboratory features and clinical follow-up, or
B) Imaging or biopsy results.

3. **Solitary extracranial GCA**: evidence of large-artery inflammation, assessed by biopsy or imaging, in patients over 50 years of age without clinically apparent cranial GCA, irrespective of the results of temporal artery biopsy.

Articles reporting on groups 2 and 3 were included. It has to be noted, though, that patients without clinically apparent cranial GCA may still have cranial involvement, which cannot be excluded even with temporal artery biopsy due to limited sensitivity. The main objective of this study was to summarise knowledge on extracranial GCA, irrespective of cranial involvement. Studies on patients with Takayasu arteritis were not included. Although both diseases are sometimes considered to represent a spectrum of the same disease entity, Takayasu patients are, by definition, younger and characteristics of these patients and their disease may be different than for GCA. Epidemiology, histopathology, signs and symptoms, diagnosis, treatment and complications will be discussed. As there is no current literature on pathogenesis, this topic will not be reviewed.

**Epidemiology**

**Cranial GCA with established extracranial involvement**

Extracranial involvement in patients with cranial GCA is likely underestimated in early retrospective studies, as patients were not systematically analysed for extracranial involvement. If only the symptoms are considered, the prevalence of extracranial involvement was traditionally estimated at 3-15%. Clues pointing to a higher prevalence of extracranial involvement were first found in a small post-mortem study showing aortic inflammation in 12 of 13 (92%) patients with temporal arteritis. Current estimates are largely based on imaging studies. The highest rate (83%) of extracranial involvement was found in a study using very liberal diagnostic criteria: any degree of uptake of 18-fluorodeoxyglucose (18F-FDG) on positron emission tomography (PET) in large arteries. Most prevalence studies, however, have included small numbers of patients and suffer from selection bias, e.g. non-consecutive series, imaging performed at the discretion of the physician or imaging of only symptomatic patients. In addition, several series combine results of extracranial involvement in patients with cranial GCA and solitary extracranial GCA. Table 1 displays an overview of reported prevalences. The aorta and its proximal branches appear to be involved most frequently, although the aorta itself was not studied in all series, namely when ultrasound was used as imaging modality. Lower extremities are less often affected although probably more frequently than previously thought.

**Solitary extracranial GCA**

No study has systematically evaluated the prevalence of solitary extracranial GCA. The largest post-mortem population study published (performed in Scandinavia in 889 consecutive patients, six-month selection period, median age 75 (range 39-90) years) suggested a prevalence of extracranial GCA of 1.4-1.7%; only one fifth of these patients had a prior clinical diagnosis of cranial GCA. Additionally, series in patients undergoing large-artery surgical procedures, e.g. after aortic dissection or aneurysm, have revealed a high number of cases with extracranial GCA; the prevalence ranged from 1 to 8.4%. Although these series are highly biased by selection, they illustrate that the prevalence of solitary extracranial GCA is higher than previously considered. In addition, extracranial GCA is suspected in 17-25% of elderly patients with fever or elevated erythrocyte sedimentation rate (ESR) of unknown origin. Few
epidemiological data are available to characterise extracranial GCA patients. However, compared with cranial GCA, they seem to be characterised by a higher proportion of women, a younger age at disease onset, and a longer diagnostic delay.\(^6,20,21\) Taken together, the true prevalence and incidence of extracranial GCA is unknown, but recent data suggest it may be much higher than the currently estimated incidence of GCA, which is only 1.6-32.8 per 100,000.\(^22,23\)

**Histopathology**

Microscopically, extracranial and temporal artery specimens are similar.\(^24\) Histological features include intimal thickening and granulomatous inflammation, including lymphocytes and giant cells, often in close proximity to a fragmented elastic lamina (figure 2). In atypical cases, inflammation and medial thickening are moderate and scattered, and dense medial fibrosis is a hallmark.\(^25\) Giant cells are found described, qualitatively, as occurring in a variable number) primarily in the media, and some in the intima.\(^6,25\) In the quiescent chronic phase, infiltrates and giant cells become scanty.\(^27\)

**Clinical signs and symptoms**

General and cardiovascular signs and symptoms may be encountered in patients with extracranial GCA. The quality of the literature, e.g. small, selected or mixed series, precludes accurate estimates of the prevalence of the various signs and symptoms. However, a couple of conclusions can be drawn.

 Patients may be completely asymptomatic and be identified, for example, after an elevated ESR was found during routine examination or after vascular, e.g. aortic surgery.\(^48\) An aortic insufficiency murmur may indicate the presence of aortic aneurysm.\(^6\)

Non-specific symptoms that are considered to be more common in extracranial GCA, with reported prevalences if known between brackets, include malaise, fever (10-61%), weight loss (20%), anorexia, polymyalgia (0-40%) and muscle weakness.\(^6,29\) Vascular symptoms such as limb claudication, Raynaud’s phenomenon, digital ischaemia, decreased pulses, arterial bruits and signs of cerebral ischaemia are more specific, but are considered less common manifestations of extracranial GCA (prevalences not reported).\(^13,29-31\)

Symptoms that are more suggestive of cranial GCA such as headache, in some series published as non-specific headache, and polymyalgia rheumatica are reported in 0-10% and 0-40% of cases, respectively.\(^6,29,32\)

In conclusion, extracranial GCA should be considered in elderly patients presenting with elevated inflammatory markers in combination with either non-specific symptoms or peripheral arterial disease without overt atherosclerosis. Refractory disease should also raise suspicion of extracranial involvement.\(^33\)

**Diagnosis**

(Solitary) extracranial GCA is often difficult to diagnose due to non-specific signs and symptoms. Also, affected arteries are frequently inaccessible for biopsy.\(^39\) As a result, and also because of a lack of awareness of this disease, an extensive (average up to six months) diagnostic delay may occur, particularly in solitary extracranial GCA, with concomitant morbidity and risk of complications.\(^6,27\)

**Laboratory studies**

There is no specific laboratory test for extracranial GCA. Inflammatory parameters (ESR, C-reactive protein) are considered sensitive for GCA, but their exact sensitivity is unknown.\(^3,8,37\) In cranial GCA, normal inflammatory

---

**Table 1. Overview of reported extracranial involvement in patients with cranial GCA**

<table>
<thead>
<tr>
<th>Arterial segment</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aorta</td>
<td>45-65%</td>
</tr>
<tr>
<td>Thoracic</td>
<td>12-45%</td>
</tr>
<tr>
<td>Ascending</td>
<td>12-45%</td>
</tr>
<tr>
<td>Aortic arch</td>
<td>5%</td>
</tr>
<tr>
<td>Descending</td>
<td>Unknown</td>
</tr>
<tr>
<td>Abdominal</td>
<td>37-54%</td>
</tr>
<tr>
<td>Cerebral</td>
<td>17-62%</td>
</tr>
<tr>
<td>Carotids</td>
<td>8-17%</td>
</tr>
<tr>
<td>Vertebro-basilar</td>
<td>8-17%</td>
</tr>
<tr>
<td>Extremities</td>
<td></td>
</tr>
<tr>
<td>Subclavian</td>
<td>26-100%</td>
</tr>
<tr>
<td>Axillary</td>
<td>18-44%</td>
</tr>
<tr>
<td>Iliac</td>
<td>15-62%</td>
</tr>
<tr>
<td>Femoral</td>
<td>12-53%</td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>8-25%</td>
</tr>
<tr>
<td>Coronary</td>
<td>Unknown</td>
</tr>
<tr>
<td>Mesenteric</td>
<td>18-23%</td>
</tr>
<tr>
<td>Any type of large vessel involvement</td>
<td>68-83%</td>
</tr>
</tbody>
</table>

**Figure 2. Haematoxylin and eosin stain at 200x magnification. Aortic (A) and temporal artery (B) biopsy showing dense lymphocytic infiltration of the intima (white ovals) and occasional giant cells in the media (red squares)**
parameters are found in up to 4% of cases. Whether the data are similar for solitary extracranial GCA is unknown. Whether the level of inflammation is informative, and whether levels in extracranial GCA are higher than in solitary cranial GCA is controversial.

Imaging

Because signs, symptoms and blood tests are non-specific and affected arteries are difficult to biopsy, the diagnosis of extracranial GCA often relies on imaging. Several imaging modalities are used in clinical practice, all comprising advantages and limitations. An important challenge is to differentiate extracranial GCA from atherosclerotic inflammation.

Conventional angiography used to be the gold standard for diagnosing extracranial GCA. However, at present, it is no longer indicated as it has been replaced by non-invasive imaging modalities.

Ultrasonography of the affected arteries may reveal homogeneous hypo-echoic swelling of the arterial wall, or stenosis during Doppler ultrasonography (≥ 1.5 mm wall thickness/oedema in the proximal branches of the aorta is regarded to be diagnostic); the thoracic aorta is more difficult to investigate due to the anatomic location below bone and air. Cut-off values for temporal arteries and aorta have not been described. Areas that are also affected by atherosclerosis are more heterogeneous, and sometimes hyper-echoic. In a small study, contrast-enhanced ultrasound was recently suggested to be a marker of disease activity.

Computed tomographic angiography (CTA) and magnetic resonance angiography display vessel wall thickening, oedema, and mural contrast enhancement. Recently, a protocol for dynamic contrast-enhanced MRI was introduced. The mean extraction of gadolinium, a measure of inflammation, was significantly higher in patients with arteritis compared with controls (suspected of arteritis, but no diagnosis could have been established), and highly correlated with 18F-FDG uptake. This technique has to be further explored.

18F-FDG-PET visualises glucose uptake (whole body assessment) by metabolically active cells. Quantitative (metabolic rate of glucose) or semi-quantitative (standardised uptake value) measurements of 18F-FDG uptake in the vessel wall are hampered by partial volume effects, causing overestimated or underestimated FDG uptake, depending on spill-over from or to adjacent regions. Standardised uptake values have been shown to correlate with acute-phase reactants and serum IL-6 concentrations, and may thus correlate to disease activity. Nevertheless, due to the aforementioned limitations, a qualitative rather than quantitative assessment of 18F-FDG uptake is generally used.

A recent study suggested that adding 18F-FDG-PET to routine clinical assessment significantly increased diagnostic accuracy. The results of this study should be interpreted with caution as the value of this study may be limited by the fact that the results of 18F-FDG-PET were part of the reference diagnostic criteria.
Because all imaging modalities have limitations, hybrid imaging such as combining $^{18}$F-FDG-PET with CT angiography or magnetic resonance angiography may have additional potential for the diagnosis of extracranial GCA. However, such an approach has not yet been studied.

**Proposed choice of imaging modality in patients suspected of extracranial GCA**

Although all modalities lack solid formal evaluation studies to address diagnostic criteria and diagnostic characteristics, the literature does provide suggestions for a recommended imaging strategy.

Ultrasound (widely available, low costs, no side effects) of the arteries of the proximal arm showed high agreement with MRI and $^{18}$F-FDG-PET. However, ultrasonography is operator-dependent and unable to depict structures beneath bone or air, such as the aorta.

A prospective study suggested that MRI is roughly as sensitive as $^{18}$F-FDG-PET(CT), although more affected vascular segments were detected using $^{18}$F-FDG-PET. Moreover, $^{18}$F-FDG-PET images inflammation rather than morphology, and would thus be expected to better correlate with disease activity.

The most obvious choice of imaging modality in patients will depend on which signs and symptoms initially raised suspicion of extracranial GCA. Three scenarios are most common (figure 5):

- Firstly, patients may present with signs and symptoms suggesting cranial GCA. The initial step is to perform temporal artery biopsy or, depending on local expertise, ultrasonography of the temporal artery and/or proximal branches of the aortic arch. In other cases, or when ultrasound and/or biopsy is normal, $^{18}$F-FDG-PET(CT) seems an appropriate next step, although CTA and MRI are reasonable alternatives. Larger, prospective, studies should compare which modality has the best diagnostic accuracy and prognostic significance in these cases.

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**Table 2. Reported CT and $^{18}$F-FDG PET criteria for the assessment of large-vessel vasculitis/aortitis. (CT in bold, PET in italic)**

<table>
<thead>
<tr>
<th>CT or $^{18}$F-FDG PET criteria</th>
<th>Positive if</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic wall thickness</td>
<td>&gt; 2 mm without adjacent atherosclerotic plaque (or aortic aneurysm or ectasia)</td>
</tr>
<tr>
<td>Grading systems</td>
<td>≥ 3 mm circumferential in absence of adjacent atherosclerotic plaque</td>
</tr>
<tr>
<td>0: no visualisation of blood vessels</td>
<td>≥ 2 mm circumferential in areas without adjacent atheroma</td>
</tr>
<tr>
<td>1: minimal vessel uptake</td>
<td>&gt; 1 mm in aortic branches</td>
</tr>
<tr>
<td>2: increased vessel uptake</td>
<td>Grade 2 and 3</td>
</tr>
<tr>
<td>3: marked vessel uptake</td>
<td>A total vascular score was derived by adding scores for 7 regions. No threshold for 'positive/negative'.</td>
</tr>
<tr>
<td>0: no uptake</td>
<td>No diagnostic threshold reported</td>
</tr>
<tr>
<td>1: low-grade uptake (lower than liver)</td>
<td>Any visible FDG-uptake in the aorta and/or grade ≥ 2 uptake in aortic branches</td>
</tr>
<tr>
<td>2: intermediate-grade uptake (similar to liver uptake)</td>
<td>Grade 2 or 3 uptake in thoracic aorta, and/or any visible uptake in other segments</td>
</tr>
<tr>
<td>3: high-grade uptake (higher than liver, lower or similar to brain)</td>
<td>Grade 2 or 3</td>
</tr>
<tr>
<td>Grade 2 and 3</td>
<td>Grade 3</td>
</tr>
<tr>
<td>‘Increased’ (unspecific) circumferential $^{18}$FDG uptake over a longer segment of the arterial wall.’</td>
<td></td>
</tr>
</tbody>
</table>

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**Table 2. Reported CT and $^{18}$F-FDG PET criteria for the assessment of large-vessel vasculitis/aortitis. (CT in bold, PET in italic)**

<table>
<thead>
<tr>
<th>Study</th>
<th>CT or PET criteria</th>
<th>Positive if</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agard, 2008</td>
<td>Aortic wall thickness</td>
<td>&gt; 2 mm without adjacent atherosclerotic plaque (or aortic aneurysm or ectasia)</td>
</tr>
<tr>
<td>Marie, 2009</td>
<td>Grading systems</td>
<td>≥ 3 mm circumferential in absence of adjacent atherosclerotic plaque</td>
</tr>
<tr>
<td>Prieto-Gonzalez, 2012</td>
<td>0: no visualisation of blood vessels</td>
<td>≥ 2 mm circumferential in areas without adjacent atheroma</td>
</tr>
<tr>
<td>Blockmans, 2000</td>
<td>1: minimal vessel uptake</td>
<td>&gt; 1 mm in aortic branches</td>
</tr>
<tr>
<td>Blockmans, 2006</td>
<td>2: increased vessel uptake</td>
<td>Grade 2 and 3</td>
</tr>
<tr>
<td>Both, 2008</td>
<td>3: marked vessel uptake</td>
<td>A total vascular score was derived by adding scores for 7 regions. No threshold for 'positive/negative'.</td>
</tr>
<tr>
<td>Müller, 2003</td>
<td>0: no uptake</td>
<td>No diagnostic threshold reported</td>
</tr>
<tr>
<td>Scheel, 2004</td>
<td>1: low-grade uptake (lower than liver)</td>
<td>Any visible FDG-uptake in the aorta and/or grade ≥ 2 uptake in aortic branches</td>
</tr>
<tr>
<td>Walter, 2005</td>
<td>2: intermediate-grade uptake (similar to liver uptake)</td>
<td>Grade 2 or 3 uptake in thoracic aorta, and/or any visible uptake in other segments</td>
</tr>
<tr>
<td>Fuchs, 2006</td>
<td>3: high-grade uptake (higher than liver, lower or similar to brain)</td>
<td>Grade 2 or 3</td>
</tr>
<tr>
<td>Papathanasiou, 2012</td>
<td>Grade 2 and 3</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Lehmann, 2010</td>
<td>‘Increased’ (unspecific) circumferential $^{18}$FDG uptake over a longer segment of the arterial wall.’</td>
<td></td>
</tr>
</tbody>
</table>
Secondly, extracranial GCA may be suspected in patients presenting with large-artery disease, either with or without elevated inflammatory parameters. In such cases, CTA or MRI will often be available as part of the diagnostic work-up, and may therefore be used.

Thirdly, older (i.e. > 50 years of age) patients may present with constitutional symptoms (fever, night sweats, etc). The differential diagnosis in these patients is broad, including extracranial GCA, infection and cancer, all of which may be detected by $^{18}$F-FDG-PET/CT, after routine tests have been non-diagnostic.

Regardless of the clinical scenario, the sensitivity of CTA, MRI and $^{18}$F-FDG-PET for the detection of extracranial GCA decreases during corticosteroid treatment. Therefore, we recommend that imaging is performed prior to or as soon as possible after the initiation of immunosuppressive treatment: i.e. within 24 hours, although this is merely experience based. Conceivably, this is particularly relevant for $^{18}$F-FDG-PET. If imaging studies are ordered when treatment has started and systemic inflammation has subsided, thus decreasing the sensitivity of $^{18}$F-FDG-PET, morphological studies (MRI or CTA) may be the best option.

Finally, variability in diagnostic criteria used in CTA, MRI and $^{18}$F-FDG-PET illustrate the need for standardisation of diagnostic and classification criteria. Currently, the American College of Rheumatology and European League Against Rheumatism are developing a new set of diagnostic and classification criteria for primary systemic vasculitides (clinical trials: NCT01066208).

**Biopsy**

Large arteries are usually inaccessible for biopsy unless vascular surgery is required. On routine clinical biopsy, temporal arteries are infrequently involved in solitary extracranial GCA. The sensitivity of an appropriately obtained (at least 1-1.5 cm during surgery, > 7 mm after fixation) temporal artery biopsy in extracranial GCA may be no higher than 58%. In view of reported sensitivities of 56-91% in clinically apparent cranial GCA patients, this is not surprising. Sensitivity probably depends on the presence of symptoms suggestive of temporal arteritis. Despite the risk of false-negative results, some recommend temporal artery biopsy in patients with suspected solitary extracranial GCA, as a positive result is highly specific for GCA. One could argue, however, not to biopsy when imaging results are highly suggestive of extracranial GCA.

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**Figure 5. Proposed choice of diagnostic (imaging) modalities for three distinct clinical scenarios suggesting possible large-vessel GCA**

- **I. Patients suspected of temporal arteritis**
  - TAB or (if expertise available) ultrasound of temporal artery and proximal arm arteries
  - $^{18}$F-FDG-PET/CT

- **II. Large-artery disease (aneurysm, dissection or stenosis)**
  - MRI or CTA

- **III. Constitutional symptoms with or without elevated inflammatory parameters (ESR/CRP)**
  - Routine tests: blood and urine tests (including cultures) + chest X-ray + abdominal ultrasound or CT
  - $^{18}$F-FDG-PET/CT

**TAB** = temporal artery biopsy; **MRI** = magnetic resonance imaging; **CTA** = computed tomographic angiography; **$^{18}$F-FDG-PET/CT** = $^{18}$F-fluorodeoxyglucose positron emission tomography with or without combined low-dose CT; **ESR** = erythrocyte sedimentation rate; **CRP** = C-reactive protein.
as a negative biopsy by no means excludes GCA, certainly not in large arteries.

The influence of steroids on the results of temporal artery biopsy is undetermined in extracranial GCA. Aortic biopsies of patients treated with low-dose steroids prior to surgery showed persistent features of aortitis. Prolonged steroid use tends to render pathological features less specific. Sensitivity may, however, be largely maintained as disturbed media anatomy and fragmentation of the internal elastic lamina persist.

DIFFERENTIAL DIAGNOSIS OF LARGE-VESEL VASCULITIS

When large-artery inflammation is suspected, e.g. after imaging, the differential diagnosis includes more than just GCA, particularly in the absence of cranial GCA symptoms. Both primary and secondary large-vessel vasculitides have to be considered. Primary large-vessel vasculitides mainly consists of GCA and Takayasu arteritis. Apart from age, a difference in systolic blood pressure of > 10 mmHg and arm or leg claudication are suggestive of Takayasu, whereas myalgia is more common in GCA. Histopathology is largely identical, and giant cells occur in both conditions. In addition, imaging characteristics are similar.

Secondary large-vessel vasculitis is less common and may be caused by infection, such as HIV, syphilis, tuberculosis, or hepatitis, or may occur in systemic inflammatory disease, such as rheumatoid arthritis, Behçet’s disease, Cogan syndrome, relapsing polychondritis, systemic lupus erythematosus, sarcoidosis or IgG4-related aortitis.

COMPLICATIONS AND PROGNOSIS

Most of the current knowledge on this topic is derived from studies in patients with cranial GCA, predominantly in those without prior evidence of extracranial involvement. Nevertheless, as extracranial complications did develop in these patients, inflammation in these vessels was considered to be present. The most frequent complication is arterial stenosis. However, more serious complications (aneurysm or dissection, the incidence being higher than arterial stenosis when both are combined) may occur. Moreover, sudden death from aortic rupture may be the first disease manifestation. The cumulative incidence of extracranial complications has increased significantly in recent years, most likely due to a greater awareness and an increased use of imaging techniques.

Ischaemia

Aortic arch syndrome was already reported as a complication of GCA in 1938. Aortic arch syndrome and aortic aneurysms may, in rare cases, occur simultaneously. Stenosis of arteries supplying the upper extremities occurs in 5-45% of GCA patients with extracranial involvement.

Ischaemic stroke occurs mainly due to vertebrobasilar artery involvement, although carotid arteries may also be affected. Approximately 3.7% of patients experience stroke, usually occurring between the onset of symptoms and four weeks after initiating corticosteroids. Smoking adds to the risk of vertebrobasilar stroke. Stroke may, however, also be due to cranial involvement of GCA.

Whether the risk of acute myocardial infarction is increased is unclear. In one study, 38 of 167 (23%) patients developed acute myocardial infarction after GCA or polymyalgia rheumatica was diagnosed, with male sex and presence of hypertension as additional risk factors. A large study showed that, after adjustment for cardiovascular risk factors, GCA patients had a higher risk of peripheral vascular disease (HR 1.85, 1.45-2.36) and cerebrovascular accidents (HR 1.71, 1.27-2.29) when compared with non-GCA patients. In addition, GCA was an independent risk factor for serious cardiovascular events.

Aortic aneurysm

In a relatively small follow-up study, the only study performed to date in patients with established extracranial involvement, both male and female GCA patients developed larger ascending aortic diameters than matched controls. Clinical symptoms relating to aortic aneurysm occur in only 3-13% of cases. The overall prevalence of aortic aneurysms is undetermined and probably ranges between 0-27%. Intriguingly, the geographical distribution of GCA incidence resembles that of aneurysmatic disease. The diagnosis of aneurysmal disease is usually established within the first 4-5 years after the diagnosis of GCA. Younger age, male sex, polymyalgia and hypertension are additional risk factors. The thoracic aorta is most often affected. Thoracic aortic aneurysms occur roughly equally often in the proximal ascending aorta, the aortic arch and the descending aorta. It has been suggested to screen all patients with temporal arteritis for large-artery complications (i.e. yearly CT scan or chest X-ray and abdominal ultrasound), but the yield of such a strategy is undetermined.

Finally, distal aortic events such as abdominal aortic aneurysms develop more frequently in patients previously diagnosed with large-vessel GCA. Relapse and inflammatory markers (ESR/CRP) were negatively correlated with the development of aortic structural disease in one study. These findings are remarkable as a recent study showed a higher number of relapses in patients with extracranial GCA established by imaging, suggesting these patients would be more prone to extracranial complications.
Aortic dissection
Dissection occurs more often in GCA. The exact incidence is, however, unclear. A near-complete disruption of the elastic lamina weakens the aortic wall and probably renders it prone to dissection. Hypertension and diagnostic delay increase the risk of dissection. Dissections occur at a median of 2.5 years after GCA diagnosis.

Mortality
GCA patients presenting with acute aortic pathology as the first clinical manifestation have a high mortality rate (44-80%), whether or not they have previously established extracranial involvement. Mortality is markedly increased in GCA patients in whom thoracic aortic dissections and aneurysms develop (HR 3.4; 95% CI 2.2-5.4), whereas increased mortality has not been established in patients developing other large-artery complications. In addition, a retrospective study showed that patients with extracranial GCA (aortitis) had more vascular causes of death and more vascular events, including stroke, than GCA patients without aortic involvement. Mortality due to ischaemic heart disease was higher in patients with GCA than in patients with ischaemic heart disease without GCA (HR 3.42; 95%-CI 1.85-6.33).

TREATMENT

Immunosuppressive therapy
In the absence of randomised clinical trials, the need for immunosuppressive therapy for extracranial GCA is unproven. Current data do not support a more aggressive approach as long-term outcome of patients with ‘isolated’ GCA is considered to be good. Nevertheless, no prospective trials have been performed in such patients. A more aggressive, pre-emptive treatment is supported by several non-randomised, non-controlled studies. In a study of 36 extracranial GCA patients, 11 received steroids and developed no new aneurysms, whereas six of 25 untreated patients did. In our clinical experience, general symptoms such as malaise, fever, myalgia, and anaemia often subside almost instantly in extracranial GCA patients after steroid treatment. One recent, prospective trial also showed improvement of CTA signs of vasculitis one year after treatment with glucocorticoids.

If treatment is indicated, patients are often subjected to the same regimen as cranial GCA patients. Although there is no generally accepted regimen, it is common to start with a prednisone dose of 40-60 mg (or 1 mg/kg). Gradual tapering is needed: 5 mg every 1-2 weeks until a dose of 10 mg/day is reached, after which smaller steps are indicated. There are no validated biomarkers, neither chemistry nor imaging, to assess response or relapse. The duration of therapy is highly variable, with some patients experiencing a chronic relapsing course. Osteoporosis prophylaxis and gastric protection should be considered.

Several disease-modifying anti-rheumatic drugs and biological agents have been investigated in patients with cranial GCA, and may be considered in extracranial GCA if corticosteroids are not tolerated or in steroid-refractory cases. Methotrexate, infliximab, etanercept, azathioprine, cyclophosphamide, mycophenolate, leflunomide and – more recently, showing great potential – tocilizumab have been described in patients with temporal arteritis without known large-vessel involvement, largely with conflicting results.

Surgery
Reconstructive surgery is not recommended during active inflammation, since most patients will respond to high-dose corticosteroids. Furthermore, vascular anastomoses tend to occlude when performed during active disease. The technical success rate of upper limb revascularisation ranges from 50%, in case of occlusions, to 100% in case of stenosis. Recurrent lesions mainly develop in territories of initially long-segment (> 3 cm) lesions. Repair of GCA-related aortic aneurysms seems safe and efficacious. An open procedure is preferred in patients with minor comorbidity and low expected mortality. Patients undergoing repair of ascending aortic aneurysms secondary to giant cell arteritis should undergo life-long screening evaluations of the remaining aorta, as a significant percentage require intervention for more distal disease.

AREAS OF UNCERTAINTY

Our knowledge on extracranial GCA has expanded substantially over the last years. There is no internationally accepted definition for extracranial GCA, and heterogeneity in definitions complicates comparison of studies. Although it is most likely that cranial and extracranial GCA are two entities in a spectrum, clear definitions would facilitate scientific progress in this field. Despite increased awareness, the current literature on extracranial GCA is still limited. Several uncertainties remain, two of which we believe deserve a particularly high priority. The first pertains to diagnosis and involves the question of which imaging modality is preferred, and how imaging can contribute to the establishment of a diagnostic reference standard, given the limitation that biopsy of affected arteries is often impossible. For this purpose,
Lensen et al. Extracranial giant cell arteritis.

The authors have nothing to disclose.

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Maturity onset diabetes of the young: Seek and you will find

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ABSTRACT

Maturity onset diabetes of the young (MODY) is a monogenic, autosomal dominant form of diabetes characterised by mutations in genes resulting in dysfunction of pancreatic β-cells and subsequent insulin production. We present a family with HNF1A-MODY due to a likely pathogenic mutation in HNF1A (c.59G>A, p.Gly20Glu), diagnosed a long time after the first diagnosis of diabetes. Currently 13 MODY subtypes caused by mutations in 13 genes, are known. We describe the four most prevalent forms in more detail, i.e. HNF4A-MODY, GCK-MODY, HNF1A-MODY and HNF1B-MODY, together responsible for probably 99% of MODY cases. The different forms of MODY vary in prevalence, severity of diabetes, occurrence and severity of diabetic complications and response to treatment. New tools, such as the MODY probability calculator, may be of assistance in finding those patients in whom further genetic testing for possible MODY is warranted. However, as our described family shows, a doctor’s clinical eye and taking the time for a detailed family history may be equal to, or even better than, the best prediction rule.

KEYWORDS

Diabetes mellitus, HNF1A, MODY

INTRODUCTION

Diabetes mellitus is a worldwide disease associated with microvascular and macrovascular complications and still has an increasing prevalence and incidence.¹ Although most patients with diabetes mellitus have either type 1 diabetes (~10%) characterised by primary insulin deficiency due to autoimmune β-cell destruction, or type 2 diabetes (~85%) characterised by insulin resistance and relative insulin deficiency, other types of diabetes mellitus do exist. In contrast to the more complex multifactorial origin of type 1 and type 2 diabetes mellitus, some of the less prevalent forms of diabetes have a monogenetic origin. Of these, maternally inherited diabetes and deafness with a prevalence of around 1% in de diabetic population,² and maturity onset diabetes of the young (MODY) constitute the most important diabetes subtypes. MODY comprises a distinct group of monogenic and autosomal dominant inherited forms of diabetes mellitus due to β-cell dysfunction with onset at a young age. It may be difficult to distinguish from late onset type 1 diabetes and early onset type 2 diabetes, due to the absence of clear distinguishing features at diagnosis and relatively low prevalence in the population. In the present article we set out to give an overview of MODY and describe the importance of considering and confirming the diagnosis of MODY using a family case report.

FAMILY CASE REPORT

Patient 1

Our index patient was diagnosed with gestational diabetes at the age of 31 years. Hyperglycaemia persisted after delivery and five years later a probable diagnosis of type 2 diabetes (~85%) was made. At that time her body mass index (BMI) was 25 kg/m² and a C-peptide test showed a good insulin reserve. After initial treatment with diet only, metformin was started but glucose regulation did not improve. A low dose of the sulfonylurea derivative tolbutamide was added and a few years later replaced by insulin therapy. Since the time of diagnosis, diabetic nephropathy (microalbuminuria) and peripheral

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polyneuropathy developed. Although the patient had received care at our hospital for 25 years and earlier correspondence reported a strong positive family history of diabetes mellitus and cardiovascular disease, no detailed family history was taken. A likely autosomal dominant inheritance pattern of diabetes was discerned in her extended pedigree (figure 1) and genetic testing for the presence of a mutation in the HNF1A gene was performed. The patient (proband IV-8.2 in figure 1) was heterozygous for a variant in HNF1A (c.59G>A, p.Gly20Glu) that had not been detected previously. At the age of 61 her diagnosis was therefore changed to possible HNF1A-MODY. As a consequence, her insulin was stopped and a successful sulfonylurea derivative trial was performed. At the moment her HbA1c is stable at 55 mmol/mol (7.2%) on a diet while taking gliclazide. The patient is currently not using any insulin and reports an increase in the quality of life after stopping insulin therapy.

Patient 2

The 12 years younger brother of patient 1 (subject IV-8.7 in figure 1) was diagnosed with type 2 diabetes at the age of 24 years based on obesity and preserved insulin reserve during a C-peptide test, after which therapy with NPH insulin once daily was initiated. Major complications of the diabetes developed partly due to the patient’s long withdrawal from care. The patient developed diabetic retinopathy and nephropathy before the age of 40, which progressed to end-stage renal disease, followed by bilateral Charcot feet. At age 44, intensive insulin therapy was started, while three years later gastric bypass surgery was performed because of persistent obesity (BMI approximately 40 kg/m²). After his sister’s diagnosis of HNF1A-MODY, the same HNF1A mutation was found to be present and the insulin was withdrawn. Trials with sulfonylurea derivatives and meglitinides (due to postprandial hypoglycaemia with a low-dose sulfonylurea

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**Figure 1. Pedigree of our HNF1A-MODY family**

Squares indicate male subjects, circles female subjects. Boxes with dotted lines indicate adopted subjects. I-V indicate the five different generations. The arrow indicates the index patient

- No known diabetes and no further data available
- Diabetes and genetically proven HNF1A-MODY
- Diabetes and clinically presumptive HNF1A-MODY
- Assumptive HNF1A-MODY but no available data
- Genetically proven HNF1A-mutation but no current diabetes
- No diabetes and genetically proven absence of the HNF1A mutation

IFG = impaired fasting glucose. A diagonal line through the symbol indicates that the subject has died. In the textboxes next to subjects the current age, absence or presence of diabetes with age of diagnosis (D) and absence or presence of cardiovascular disease with age of onset (CVD) are described.
derivative) were performed. Currently the patient is not using any oral glucose-lowering medication or insulin and has stable glycaemic control at 4.2 mmol/mol on a diet.

Family
The patients described here came from a large family of Dutch and part Indonesian ancestry. After the probable diagnosis of HNF1A-MODY in the two patients described above, multiple family members with early onset diabetes mellitus came forward for genetic testing. Figure 1 shows the extensive pedigree of the family with the high prevalence of early diabetes and cardiovascular morbidity and mortality and a suggestive autosomal dominant inheritance pattern. Microvascular complications were present in all the known HNF1A-MODY patients in this family, except for the recently diagnosed son of the index patient (V-8.2.1 in figure 1). The age at diagnosis of diabetes mellitus in the family was between 21 and 40 years, with one exception, who was only diagnosed after the discovery of coronary artery disease at the age of 49. All patients from the family with a prior diagnosis of type 2 diabetes were found to be heterozygous for the earlier described variant in HNF1A (table 1). Subsequently, the diagnosis in these patients was changed to HNF1A-MODY and the treating physicians were informed including advice on treatment.

In our pedigree we have 12 informative meioses in which the mutation as well as the disease segregate together. A ‘rule of thumb’ is that each meiosis in which the mutation segregates with the phenotype adds 0.3 to the total likelihood of odds (LOD) score, giving a total LOD score in our pedigree of ~3.6: > 3 is a significant association; we could add some additional informative meioses higher up in the pedigree and come to an estimated LOD score of ~5.4. The mutation carriers who have no symptoms (yet) fit in the reduced penetrance that is described for MODY (proband IV-5.11) in combination with the relatively young age of some family members (V-5.9.1, V-5.10.1 and V-5.10.2) who may still develop diabetes in the coming years and were advised to undergo yearly check-ups.

Epidemiology
The prevalence of MODY remains unknown but is estimated to be responsible for 1-5% of cases of diabetes mellitus.4-6 As MODY shares clinical features with the more common forms of diabetes mellitus, the true prevalence is probably underestimated.

At present, mutations in 13 genes linked to different types of MODY have been identified.7-9 In table 2 the currently known subtypes of MODY are described with their related proteins/genes and estimated prevalence.10-14 In general, GCK-MODY and HNF1A-MODY each represent 20-70% of all cases, HNF4A-MODY and HNF1B-MODY each account for about 5%, while the other forms are extremely rare.10-14 GCK-MODY is more commonly diagnosed in countries where glucose testing of asymptomatic people and paediatric cases is routine (Czech Republic, France, Italy, Spain), whereas HNF1A-MODY is more often diagnosed in countries where random blood glucose tests are seldom done and elevated blood glucose is first found after childhood (Denmark, the Netherlands, Norway, United Kingdom).14,15

Pathophysiology
MODY is caused by mutations resulting in pancreatic β-cell dysfunction in the production or excretion of insulin. Normally, glucose from the circulation is taken up by the β-cell through the glucose transporter type 2 (GLUT 2) on the cell membrane. The enzyme glucokinase (GCK) converts glucose into glucose-6-phosphate which then undergoes glycolysis in the mitochondria to produce adenosine triphosphate (ATP). The increase of the ATP-ADP ratio causes the closure of the β-cell

| Table 1. Features of the genetically tested family members |
|----------------|---------|---------|--------|----------------|
| Individual     | Gender  | Current age | Diabetes | HNF1A mutation |
| IV-5.8         | M       | 64        | Yes     | Yes            |
| IV-5.10        | M       | 59        | Yes     | Yes            |
| IV-5.11        | M       | 56        | No      | Yes            |
| IV-6.5         | F       | 54        | Yes     | Yes            |
| IV-8.1         | M       | 64        | No      | No             |
| IV-8.2 (index patient) | F | 63    | Yes     | Yes            |
| IV-8.4         | M       | 59        | Yes     | Yes            |
| IV-8.7         | M       | 51        | Yes     | Yes            |
| V-5.4.1        | M       | 46        | Yes     | Yes            |
| V-5.8.2        | M       | 26        | No      | No             |
| V-5.9.1        | M       | 29        | No      | Yes            |
| V-5.9.2        | M       | 25        | No      | No             |
| V-5.10.1       | M       | 23        | No      | Yes            |
| V-5.10.2       | F       | 20        | No      | Yes            |
| V-8.1.2        | F       | 30        | No      | No             |
| V-8.2.1        | M       | 33        | Yes     | Yes            |

M = male subject, F = female subject.
ATP-sensitive potassium channel ($K_{ATP}$), preventing potassium efflux, which leads to depolarisation of the membrane and subsequently causes the opening of the voltage-dependent calcium channels. The subsequent influx of calcium into the cell stimulates exocytosis of insulin-containing granules from the $\beta$-cell (figure 2). GCK-MODY can be described as disturbed $\beta$-cell glucose sensing. Mutations in the GCK gene cause a decrease in glucose metabolism in the $\beta$-cell and therefore a rightward shift of the dose-response curve of insulin secretion.

The hepatocyte nuclear factors (HNF)-4 alpha, -1 alpha and -1 beta are transcription factors that form part of a network of transcription factors that controls gene expression of the insulin gene and genes encoding proteins involved in glucose transport and metabolism. Mutations in the genes of these transcription factors lead to reduced expression of these genes in the $\beta$-cell and subsequently less insulin production and release. Additionally, HNF-1 beta plays a pivotal role in the development of the kidney, pancreas, liver and genital tract, and mutations subsequently lead to multi-organ consequences.

The variant in HNF1A found in the featured family is located in the highly conserved N-terminal HNF-1A dimerisation domain (up to frog considering 11 species). Mutations in this domain disrupt formation of the HNF-1A dimer and the functional DCoH-HNF-1A complex. These mutations strongly argue against an obligate dominant negative mode of action and support the idea that glucose homeostasis in humans is sensitive to the dose of HNF-1A.

Various in silico algorithms (prediction programs) indicate that the p.Gly20Glu variant is probably damaging. Two other pathogenic amino acid substitutions in the same codon (p.Gly20Arg and p.Gly20Ala) and 25 other different amino acid substitutions in the dimerisation domain have been described in patients with MODY 3. Additionally, the mutation was classified as likely

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### Table 2. Currently known types of maturity onset diabetes of the young with their associated mutations and clinical features

<table>
<thead>
<tr>
<th>MODY type</th>
<th>Protein/ gene</th>
<th>Relative prevalence</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hepatocyte nuclear factor-4 alpha (HNF4A)</td>
<td>− 5 %</td>
<td>Neonatal hyperinsulinaemia and hypoglycaemia with associated macrosomia, gestational diabetes, low serum levels of cholesterol, marked sensitivity to sulfonylurea derivatives</td>
</tr>
<tr>
<td>2</td>
<td>Glucokinase (GCK)</td>
<td>20-70%</td>
<td>Mild fasting hyperglycaemia throughout life, often asymptomatic, gestational diabetes, low birth weight (with unaffected mother)</td>
</tr>
<tr>
<td>3</td>
<td>Hepatocyte nuclear factor-1 alpha (HNF1A)</td>
<td>20-70%</td>
<td>Diminished renal threshold for glycosuria, marked sensitivity to sulfonylurea derivatives</td>
</tr>
<tr>
<td>4</td>
<td>Insulin promoter factor 1 (IPF1) or pancreas/duodenum homeobox protein 1 (PDX1)</td>
<td>Rare: &lt; 1%</td>
<td>Pancreatic agenesis</td>
</tr>
<tr>
<td>5</td>
<td>Hepatocyte nuclear factor-1 beta (HNF1B)</td>
<td>− 5 %</td>
<td>Renal abnormalities and insufficiency at young age, diabetes often diagnosed later, hypomagnesaemia, hyperuricaemia, pancreatic atrophy or partial agenesis, exocrine pancreatic dysfunction, liver test abnormalities, genital abnormalities</td>
</tr>
<tr>
<td>6</td>
<td>Neurogenic differentiation 1 (NEUROD1)</td>
<td>Very rare</td>
<td>Pancreatic anomalies</td>
</tr>
<tr>
<td>7</td>
<td>Kruppel-like factor 11 (KLF11)</td>
<td>Very rare</td>
<td>Pancreatic malignancy</td>
</tr>
<tr>
<td>8</td>
<td>Carboxyl-ester lipase gene (CEL)</td>
<td>Very rare</td>
<td>Exocrine pancreatic dysfunction</td>
</tr>
<tr>
<td>9</td>
<td>Paired box gene 4 (PAX4)</td>
<td>Very rare</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Insulin gene (INS)</td>
<td>Very rare</td>
<td>Neonatal diabetes</td>
</tr>
<tr>
<td>11</td>
<td>Tyrosine kinase, B-lymphocyte specific gene (BLK)</td>
<td>Very rare</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>ATP-binding cassette, subfamily C, member 8 (ABCC8)</td>
<td>Very rare</td>
<td>Neonatal diabetes, sulfonylurea derivative responsive</td>
</tr>
<tr>
<td>13</td>
<td>Potassium channel, inwardly rectifying, subfamily J, member 11 (KCNJ11)</td>
<td>Very rare</td>
<td>Neonatal diabetes, sulfonylurea derivative responsive</td>
</tr>
</tbody>
</table>
The rarer forms of MODY are caused by mutations in other nuclear transcription factors regulating pancreatic development and expression of the insulin gene, the insulin gene itself (INS-MODY), or genes of proteins involved in the ATP-sensitive potassium channel (ABCC8-MODY and KCNJ11-MODY). They also result in impaired β-cell function with reduced insulin production and/or secretion.

**CLINICAL FEATURES**

The mode of inheritance of MODY is autosomal dominant. In general, the main characteristics of MODY are the onset of diabetes at a young age with a prominent family history of diabetes in multiple generations and, but not necessarily, absence of obesity, as was shown in our HNF1A-MODY family. Patients with MODY may easily be misdiagnosed during pregnancy as gestational diabetes in the context of increased insulin resistance, as described in our index patient. It has been shown that carriers of GCK and HNF1A mutations have an increased risk of gestational diabetes mellitus.

An overview of the typical clinical features of the MODY subtypes is shown in table 2.

**TREATMENT**

Patients with HNF4A- and HNF1A-MODY are very sensitive to the effect of sulfonylurea derivatives and meglitinides. This efficacy can be explained by the binding with the sulfonylurea receptor type 1 (SUR1) subunit of the KATP causing it to close and triggering opening of the voltage-dependent calcium channels, stimulating insulin release. As meglitinides cause a smaller insulin peak and have a shorter half-life, MODY patients using a meglitinide are less susceptible to hypoglycaemia than during treatment with sulfonylurea derivatives.

Despite the efficacy of sulfonylurea derivative and meglitinide treatment most of these patients will in time require insulin as β-cell dysfunction progresses.

GCK-MODY, which is often asymptomatic and therefore diagnosed by screening, does not require treatment due to the mild and stable hyperglycaemia with a raised homeostatic set point (glycated haemoglobin (HbA1c) without treatment usually below 64 mmol/mol (8%)). It has been shown that HNF1B patients do not respond well to sulfonylurea derivatives and that they have a reduction.
in insulin sensitivity compared with HNF1A patients.\textsuperscript{40} If HNF1B patients are treated for their diabetes, the existing studies show that they generally receive insulin.

**COMPLICATIONS**

Although patients with GCK-MODY are exposed to a lifetime of, albeit limited, hyperglycaemia, microvascular and macrovascular complications in GCK-MODY seem to be limited.\textsuperscript{41} In patients with HNF1A-MODY both microvascular and macrovascular complications are very common, as was the case in our family. The prevalence is similar to that of patients with type 1 and 2 diabetes, when matched for duration and glycaemic control,\textsuperscript{42-43} while early detection and treatment may result in a reduced incidence of diabetic complications.\textsuperscript{44} It has been suggested that the full spectrum of diabetes complications may also occur in HNF4A-MODY patients, particularly retinopathy and nephropathy.\textsuperscript{45} For HNF1B-MODY it is suggested that microvascular diabetic complications are rare.\textsuperscript{11,29-34}

**CASE FINDING**

Diagnosing MODY is challenging because of the relatively low prevalence in the general population (1-5%) and shared features with other types of diabetes (table 3). Limited awareness of MODY as a separate entity and cause of diabetes outside specialist centres combined with limited time allocated to enquiring about family history further hampers correct diagnosis, family screening and treatment. A correct diagnosis of MODY might change the treatment to oral glucose-lowering medication (HNF4A-and HNF1A-MODY) or even withdrawal of medication (GCK-MODY). Secondly, certain subtypes are associated with specific medical problems entailing additional diagnostic tests and screening. Lastly, the first-degree relatives of MODY patients have a 50\% probability of the same mutation with, at least in the two most commonly occurring MODY forms, a lifetime risk of > 95\% of developing diabetes.\textsuperscript{45,46} As progression of diabetes is generally slow in MODY patients, early diagnosis and start of appropriate treatment might reduce the risk of diabetic complications as described in a Norwegian family.\textsuperscript{44} The evidence for such an approach is, however, currently lacking and is debatable in light of the possible financial consequences for subjects with a suggestive genotype, but in the absence of diabetes. In general, two simulation studies show that screening may be cost-effective.\textsuperscript{47-48} Several suggestions have been published for when to consider genetic testing for MODY. Current European guidelines are highly specific, but have a low sensitivity.\textsuperscript{49} Correspondingly, widening of the clinical criteria for genetic testing can double the number of MODY diagnoses.\textsuperscript{50} Other recent literature describes additional criteria and Thanabalasingham et al. and Naylor et al. provided algorithms for the consideration of genetic testing.\textsuperscript{14,51,52} In 2012 a novel approach to correctly allocate genetic testing in Caucasian patients with an onset of diabetes before the age of 35 was published.\textsuperscript{53} This clinical prediction rule is available as an online calculator (www.diabetesgenes.org/content/mody-probability-calculator). Using the optimal cut-offs, it has an improved specificity (94\% vs 91\%) and especially sensitivity (91\% vs 72\%) for identifying MODY, compared with the criteria of diagnosis < 25 years and a parent with diabetes. Interestingly, applying the calculator to our patients would have advised

<table>
<thead>
<tr>
<th>Table 3. Comparison of the clinical and biochemical features of the most common types of diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Features</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Age of diagnosis</td>
</tr>
<tr>
<td>Diabetic ketoacidosis</td>
</tr>
<tr>
<td>Insulin dependent</td>
</tr>
<tr>
<td>Parental history of diabetes</td>
</tr>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td>Insulin resistance</td>
</tr>
<tr>
<td>Presence of β-cell antibodies</td>
</tr>
<tr>
<td>C-peptide concentrations</td>
</tr>
<tr>
<td>Optimal first line treatment</td>
</tr>
</tbody>
</table>
Table 4. Clinical features suggestive for maturity onset diabetes of the young

<table>
<thead>
<tr>
<th>Clinical features suggestive for MODY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any of the following:</strong></td>
</tr>
<tr>
<td>• Diabetes diagnosed ≤ 30 years</td>
</tr>
<tr>
<td>• Diabetes diagnosed ≤ 45 years in people without obesity/ insulin resistance/ metabolic syndrome</td>
</tr>
<tr>
<td>• Diabetes diagnosed ≤ 45 years and a family history of diabetes in ≥ 2 generations in an autosomal dominant fashion</td>
</tr>
</tbody>
</table>

| And in absence of:                  |
| • Diabetic ketoacidosis             |
| • Pancreatic islet autoantibodies   |
| • No endogenous insulin production outside the honeymoon period of about 3 years (e.g. undetectable C-peptide) |

Additionally, specific features of MODY subtypes may justify genetic testing:

• Glycosuria at blood glucose levels < 10 mmol/l (HNF1A-MODY)
• Marked sensitivity to sulfonylurea derivatives (HNF1A / HNF4A-MODY)
• Diabetes associated with extra pancreatic features: non-diabetic renal disease, renal anomalies, genital anomalies, abnormal liver function tests (HNF1B-MODY)

In Table 4 we have combined features and algorithms suggestive of possible MODY from the available literature, providing an optional tool for deciding on genetic testing.

**CONCLUSION**

Maturity onset diabetes of the young (MODY) encompasses distinct clinical entities causing diabetes. Our presented family illustrates the difficulties in diagnosing MODY, the consequences for treatment with the correct diagnosis as well as the long-term consequences. Correct identification of patients with MODY will probably lead to earlier diagnosis, family screening, earlier and correct treatment and hopefully improved prognosis.

**Disclosures**

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**REFERENCES**


Has dementia research lost its sense of reality?
A descriptive analysis of eligibility criteria of Dutch dementia research protocols

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ABSTRACT

Background/objectives: A substantial proportion of dementia patients are excluded from research participation, while for extrapolation of the study findings, it is important that the research population represents the patient population. The aim of this study is to provide an analysis of dementia research and its exclusion criteria in order to get a clearer picture whether the research participants represent the general dementia population.

Methods: Dementia studies registered at ToetsingOnline.nl between 2006-2015 were analysed. Study characteristics, funding and eligibility criteria were described and analysed using a standardised score sheet.

Results: The search yielded 103 usable study protocols. The number of trials has increased over the years, and 35% of the studies were industry-financed. Alzheimer’s disease was the most researched type of dementia (84%). In observational studies the most frequently observed exclusion criterion is a neurological condition, while in drug studies and other intervention studies this is a somatic condition. Of all protocols, 86% had at least one exclusion criterion concerning comorbidity. Most studies focused on mild or moderate dementia (78%).

Conclusion: Our study has shown that the distribution of dementia research over the different subtypes of dementia does not correspond with the prevalence of these subtypes in clinical practice. The research population in the protocols is not representative of the larger patient population. A greater number of dementia patients could derive benefit from the conducted research if the research agenda were more closely aligned with disease prevalence. A better representation of all dementia patients in research will help to meet the needs of these patients.

KEYWORDS

Dementia, cognitive impairment, research with vulnerable populations, clinical trials

INTRODUCTION

Research with dementia patients brings about some unique challenges that may hamper the generalisability of the study findings. In research with elderly patients age, comorbidities and sensory impairment are often used exclusion criteria. Regarding multimorbidity, it is estimated that 55-98% of patients older than 65 have two or more chronic conditions. Most people suffering from dementia are over 70 years of age. Thus, a substantial proportion of patients with dementia are excluded from study participation. As a consequence, the participants in dementia research may not represent the general dementia population. If the validity and generalisability of the findings from biomedical research are weak, patients cannot benefit from the findings of these studies.

The population of patients with dementia is challenging: the group is heterogeneous with regards to the type of dementia, severity of disease and presence of comorbidities. It also means that adjusted research methods, such as subgroup analysis, are required and extrapolation of the findings remains uncertain.

The aim of this study is to analyse study and population characteristics of dementia research protocols in the Netherlands between 2006 and 2015. Particularly, we analysed eligibility criteria in order to get a clearer picture.
as to whether the general population and the research population are concordant.

MATERIALS AND METHODS

Search strategy
We searched for dementia research protocols on ToetsingOnline.nl, the Dutch online assessment portal of the Central Committee on Research Involving Human Subjects and of the accredited Medical Research Ethics Committees. The ToetsingOnline database contains all biomedical studies conducted in the Netherlands that are reviewed by a Research Ethics Board. The trial data are self-reported by trial sponsors or investigators. Each record contains a set of data elements describing the study’s purpose, design, eligibility criteria, location, sponsor and other protocol information, although not all fields are mandatory and publicly accessible. In March 2015, we searched for all approved protocols regarding dementia between 2006-2015 including the term dementia, cognitive decline, Alzheimer’s disease, Parkinson’s dementia, frontotemporal dementia, and vascular dementia.

Data extraction
Data extraction was conducted by using a data extraction form. This form was developed in order to standardise data extraction, on the basis of a pilot assessment of a random selection of 30 protocols by the two investigators together (KJ and RB). All remaining protocols were scored by two researchers (KJ and RB) independent of each other. Disagreements that arose were solved by discussing the protocol together. The main outcome measures were: type of dementia (Alzheimer’s disease, vascular dementia, Parkinson’s dementia, familial dementia, frontotemporal dementia, Lewy body dementia, mild cognitive impairment (MCI)), type of study (observational, drug intervention, other interventions), expected number of participants, and their age, comorbidities (somatic, psychiatric, neurological and any psychiatric comorbidity). We did not score substance abuse (34 in total) as a psychiatric exclusion criterion, Alzheimer in Down syndrome patients is scored as Alzheimer research (2 studies in total), the living environment criterion was divided into dependent (institutionalised patients, being taken care of by care professionals 24/7) and independent (either living at home or at an assisted-living facility, care by a proxy and under supervision of a GP).

Descriptive analysis
We excluded studies that investigated interventions for proxies, studies not primarily focused on dementia, or prolongations of an earlier study, because the eligibility criteria were not described in the prolongation protocol. In the analysis we focused on the description of the type of studies and on the eligibility criteria for participants. Descriptive statistics were used to describe the study and participant characteristics. Categorical variables were reported as proportions and continuous variables as ranges or absolute numbers. Due to the descriptive nature of the study, formal statistical comparisons were not made.

RESULTS

Search results
The combination of search terms yielded 150 protocols. The duplicates were removed and 135 distinctive research protocols remained. From these 135 protocols, 20 studies were excluded. Thus, 115 studies remained of which 12 were drug studies with healthy volunteers and 103 with dementia or MCI patients (figure 1).

Characteristics of the protocols

Dementia protocols
The total number of participants between 2006 and 2015 (excluding healthy volunteers) was n = 26,422, ranging from 12 to 2,400. In comparison, in the year 2014 alone, 427,500 research participants were included in any study to any disease in the Netherlands.1 A substantial proportion of the dementia protocols (36%) concerned relatively small studies, enrolling 100 subjects or less. Almost half the studies are mono-centre studies, a third of the studies included participants from at least one country outside of the Netherlands (table 1). Of the 103 studies with dementia patients, 30 were drug trials, 29 other intervention studies and 44 observational studies. In total 35% of the studies were financed by the industry (table 1). Of the studies sponsored by the industry, 62% concerned drug-intervention studies.
Healthy volunteers
The studies with healthy volunteers were 11 drug-intervention studies and one observational study. The number of participants ranged from 4 to 74, with a total of 422 participants. All of these studies but one were financed by the industry and focused on Alzheimer’s disease. These protocols with healthy volunteers are not further described or analysed in this paper.

Number and type of studies over the years
A notable trend is that the total number of research protocols seems to be increasing, in total 11 protocols were reviewed in 2006-2007, compared with 34 in 2014-2015; especially drug trial research has grown tremendously over the past years (table 1 and figure 2). The industry has initiated more research trials in the last few years: 18 trials in 2014-2015 compared with one in 2006-2007. In all publication years, Alzheimer’s disease was the most researched specified type of dementia.

Type of dementia
What is remarkable is that a substantial proportion of studies (32%) do not specify the type of dementia studied (in figures and tables labelled as all dementias), while the types of dementia vary tremendously in terms of severity, symptoms and needed care. MCI/prodromal dementia composes 12% of the studies; 9% studied two or more types of dementia, all of these included Alzheimer’s disease. Of the studies focusing specifically on one type of dementia, Alzheimer’s disease is the type of dementia most often studied in terms of number of trials (84%) and in expected number of participants (13,011).

By contrast, only a small number of studies focused on vascular and Lewy body dementia; familial dementia was not studied in any of the protocols (figures 3 and 4). Most drug trials and observational studies concerned Alzheimer’s disease, and most non-drug interventions were aimed at an unspecified group of dementia patients (table 1).

Eligibility criteria used in the Dementia study protocols
Age
Regarding age, we found that 60% of the studies use age as an eligibility criterion, either an upper limit alone (7 protocols), a lower limit alone (28 protocols) or an age range (27 protocols). The range of the upper limit is 60-100 years, with an average of 83.7 years. The lower age limit ranged from 18-65 with an average of 49.1 years.

Competence
Of the studies, 24% noted competence of the research participant in their inclusion criteria, while 49% demanded the consent of the patient (implying participant’s competence). The consent of a proxy was required in 24% of the protocols, 23% asked for both proxy

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*Figure 1. Flowchart of search results*
Table 1. Overview of study and eligibility criteria

<table>
<thead>
<tr>
<th>STUDY CHARACTERISTICS</th>
<th>Alzheimer’s disease (n = 43)</th>
<th>MCI (n = 12)</th>
<th>Vascular dementia (n = 1)</th>
<th>Frontotemporal dementia (n = 4)</th>
<th>Lewy Body dementia (n = 1)</th>
<th>Parkinson (n = 2)</th>
<th>All types of dementias (n = 33)</th>
<th>Two or three types of dementia (n = 9)</th>
<th>Total (n = 103)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>21 (49)</td>
<td>4 (33)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (100)</td>
<td>1 (50)</td>
<td>11 (33)</td>
<td>5 (56)</td>
<td>44 (43)</td>
</tr>
<tr>
<td>%</td>
<td>49</td>
<td>33%</td>
<td>0%</td>
<td>0%</td>
<td>100%</td>
<td>50%</td>
<td>33%</td>
<td>56%</td>
<td>43%</td>
</tr>
<tr>
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<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (50)</td>
<td>1 (3)</td>
<td>3 (33)</td>
<td>27 (26)</td>
</tr>
<tr>
<td>%</td>
<td>47</td>
<td>42%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>50%</td>
<td>3%</td>
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<td>26%</td>
</tr>
<tr>
<td>N</td>
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<td>1 (8)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (100)</td>
<td>1 (11)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>%</td>
<td>14</td>
<td>8%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>100%</td>
<td>11%</td>
<td>6%</td>
</tr>
<tr>
<td>N</td>
<td>23 (53)</td>
<td>7 (58)</td>
<td>0 (0)</td>
<td>2 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>32 (97)</td>
<td>9 (33)</td>
<td>34 (33)</td>
</tr>
<tr>
<td>%</td>
<td>53</td>
<td>58%</td>
<td>0%</td>
<td>100%</td>
<td>0%</td>
<td>0%</td>
<td>97%</td>
<td>33%</td>
<td>33%</td>
</tr>
<tr>
<td>N</td>
<td>17 (40)</td>
<td>4 (33)</td>
<td>1 (100)</td>
<td>0 (0)</td>
<td>1 (100)</td>
<td>0 (0)</td>
<td>18 (55)</td>
<td>6 (18)</td>
<td>24 (23)</td>
</tr>
<tr>
<td>%</td>
<td>40</td>
<td>33%</td>
<td>100%</td>
<td>0%</td>
<td>100%</td>
<td>0%</td>
<td>55%</td>
<td>18%</td>
<td>23%</td>
</tr>
<tr>
<td>Number of participants</td>
<td>13011 (11)</td>
<td>570 (60)</td>
<td>30 (100)</td>
<td>210 (100)</td>
<td>60 (100)</td>
<td>700 (100)</td>
<td>6306 (100)</td>
<td>935 (97)</td>
<td>26422 (100)</td>
</tr>
<tr>
<td>Mono</td>
<td>17 (40)</td>
<td>4 (37)</td>
<td>0 (0)</td>
<td>1 (100)</td>
<td>0 (0)</td>
<td>1 (100)</td>
<td>18 (55)</td>
<td>6 (18)</td>
<td>24 (23)</td>
</tr>
<tr>
<td>Multicentre</td>
<td>7 (16)</td>
<td>1 (8)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (100)</td>
<td>2 (22)</td>
<td>23 (22)</td>
</tr>
<tr>
<td>International multicentre</td>
<td>19 (44)</td>
<td>7 (16)</td>
<td>0 (0)</td>
<td>2 (100)</td>
<td>1 (100)</td>
<td>2 (100)</td>
<td>2 (6)</td>
<td>1 (11)</td>
<td>34 (33)</td>
</tr>
</tbody>
</table>

ELIGIBILITY CRITERIA

| Sensory deficit     | 12 (28)                    | 1 (8)       | 0 (0)                    | 0 (0)                         | 1 (100)                  | 1 (50)          | 8 (24)                       | 0 (0)                           | 23 (22)        |
| Medication use      | 20 (46)                    | 6 (50)      | 1 (100)                  | 1 (100)                       | 0 (0)                    | 1 (50)          | 5 (15)                       | 5 (15)                          | 35 (33)        |
| Psychiatric         | 29 (67)                    | 9 (75)      | 1 (100)                  | 2 (100)                       | 1 (100)                  | 1 (50)          | 9 (27)                       | 5 (15)                          | 34 (33)        |
| Somatic             | 27 (63)                    | 9 (75)      | 1 (100)                  | 2 (100)                       | 1 (100)                  | 1 (50)          | 12 (36)                      | 5 (15)                          | 37 (35)        |
| Neurological        | 32 (74)                    | 9 (75)      | 0 (0)                    | 2 (100)                       | 1 (100)                  | 2 (100)         | 8 (24)                       | 4 (12)                          | 61 (60)        |
| Age criterion       | 32 (74)                    | 10 (83)     | 0 (0)                    | 2 (100)                       | 1 (100)                  | 2 (100)         | 12 (36)                      | 3 (11)                          | 62 (60)        |
| Living situation    | 8 (19)                     | 1 (8)       | 1 (100)                  | 2 (100)                       | 0 (0)                    | 0 (0)           | 22 (67)                      | 0 (0)                           | 34 (33)        |
| stated as criterion |                           |             |                         |                               |                         |                 |                               |                                 |                |
| Competence          | 12 (28)                    | 2 (17)      | 1 (100)                  | 2 (100)                       | 0 (0)                    | 0 (0)           | 5 (15)                       | 3 (11)                          | 26 (25)        |
| Informed consent    | 24 (56)                    | 6 (50)      | 1 (100)                  | 2 (100)                       | 0 (0)                    | 0 (0)           | 9 (27)                       | 6 (18)                          | 50 (49)        |
| Proxy consent       | 10 (23)                    | 3 (25)      | 0 (0)                    | 2 (100)                       | 0 (0)                    | 1 (50)          | 6 (18)                       | 3 (11)                          | 23 (22)        |
| Caretaker required  | 24 (56)                    | 5 (42)      | 1 (100)                  | 2 (100)                       | 0 (0)                    | 1 (50)          | 14 (42)                      | 5 (15)                          | 50 (49)        |
| Use of diagnostic tests | 34 (79)                  | 6 (50)      | 1 (100)                  | 2 (100)                       | 0 (0)                    | 1 (50)          | 13 (39)                      | 8 (24)                          | 65 (63)        |

and informed consent. In approximately half of the studies (51%), having a proxy was required to be included in the research, even if their consent was not necessary.

**Living situation**

Dementia patients living in nursing homes were explicitly excluded from 22% of the studies. Only a small proportion of the studies (13%) focused explicitly on patients living in nursing homes due to dementia. All other studies either recruited people living independently or did not mention the living situation as an eligibility criterion. Due to other recruitment demands, patients living in nursing homes were nevertheless excluded from these studies. For instance, in 23 studies cognitive
screening tools were used with scores implying mild or moderate dementia.

Dementia-screening instrument
A dementia-screening instrument, such as the Mini Mental State Examination (MMSE) and Clinical Dementia Rating (CDR) was used in 62% of the protocols. MMSE is most often used, and there is a large variety in the range set for eligibility, ranging between 10-30. Some studies set no lower limit at all for the MMSE score, but these studies required that the patient should live independently, thereby implicating a MMSE score of at least 10. Most studies consider patients with a MMSE score of 10 or less as severely demented.

Dementia severity
Severely demented patients were excluded from most protocols: 16 protocols focused on MCI or mild dementia and 52 protocols excluded patients with a CDR score > 2 or MMSE < 10. Of the remaining 35 protocols, five required competence of the research participant and seven required that the participant was living independently, which are unlikely conditions for severely demented patients. In the remaining 23 protocols (22%), severely demented patients may be enrolled unless they have non-eligible comorbidities.

Comorbidity and medication use
Concerning comorbidities, 22% of the studies noted a visual or hearing impairment as an exclusion criterion. Medication use was stated as an exclusion criterion in 38% of the protocols. In 54% of the studies, patients with a psychiatric disorder were excluded. Somatic comorbidities were indicated as an exclusion criterion in 54% studies; 56% excluded patients with neurological conditions. In 9% of the protocols all these five exclusion criteria were noted and 14% noted none of these exclusion criteria. The most often mentioned exclusion criterion in observational studies is a neurological condition other than dementia, while in both drug studies and other intervention studies the most often used exclusion criterion is a somatic condition.

Ambiguous criteria
A remarkable finding is that 15% of the dementia studies explicitly state very ambiguous exclusion criteria, such as ‘Any other condition that in the opinion of the investigator would complicate or compromise the study’, or ‘investigator’s uncertainty about willingness, ability, or medical status of the patient to comply with protocol requirements’ which leaves much room for interpretation by the researcher without the further intervention of a Research Ethics Board. Most of these studies were drug trials initiated by the industry.
DISCUSSION

This analysis provides a first snapshot of the landscape of dementia research and of dementia research participants as listed on ToetsingOnline in the Netherlands. The results of these research studies provide the basis for treatment and prevention for Dutch dementia patients. From this report of research trials in dementia patients, several noteworthy observations emerge.

Study characteristics

There is a discrepancy between the focus of the research trials and the prevalence rate of the different types of dementia. The estimated prevalence of Alzheimer’s disease, as reported in the literature, varies between 30 and 75% of all dementia patients. The WHO estimates that Alzheimer’s disease accounts for approximately 41% of all dementias and vascular dementia for 32%. Stevens et al. reported a prevalence of 31% Alzheimer’s disease.
22% vascular dementia, 3% Parkinson’s dementia, 8% frontotemporal dementia and 11% Lewy body dementia. As our data have shown, a disproportionate number of research trials, which specified the subtype of dementia, focus on Alzheimer’s disease (figure 4).

Mixed pathologies are common in practice, and it is not always easy to distinguish clinically between the types of dementia. This is especially true for Alzheimer’s disease and vascular dementia, and Alzheimer’s disease and Lewy body dementia. The nine study protocols that studied two or three types of dementia did aim to differentiate between subtypes of dementia. The 33 studies that enrolled patients with all types of dementia did not make that distinction, disregarding the necessity of an appropriate diagnosis of type of dementia to tailor future cure and care. Although different types of dementia are described in the literature, it is not always possible to distinguish the specific types of dementia in a single patient. In the studied protocols, it was not always described on what ground a dementia subtype was diagnosed; since the goal of our study is to sketch the landscape of scientific research regarding dementia, we have followed the assumptions made regarding subtypes of dementia.

In addition, our study suggests that the number of industry-sponsored trials has increased over the past years. These mostly focused on drug trials concerning Alzheimer’s disease and MCI. Not many trials focused on vascular dementia, Parkinson’s dementia, Lewy body dementia and none on familial dementia. The number of participants in these few studies was also fairly low, implying these types of dementia are comparatively understudied in the Netherlands. The Lewy body dementia and vascular dementia studies were conducted as mono-centre studies in the Netherlands, thus for each of these subtypes of dementia, only one single institute has studied these conditions in the past ten years. Although small trials are necessary in some cases (e.g., early-phase drug studies, trials of rare/orphan diseases), obtaining clinically meaningful and generalisable information from small studies may be difficult.

Clinical research is reported to undergo the same globalisation process as other industries and sciences, especially in the realm of clinical trials. Our data showed that 32% of the studies enrolled patients in at least one country outside of the Netherlands. Cooperation between centres (multicentre research) is considered beneficial, because it contributes to the generalisability of the patient population. Multicentre research can also contribute to the inclusion of sufficient participants, which might be a challenge in a population as heterogeneous as dementia patients. However, the living and care conditions vary tremendously in different countries, which can complicate multicentre international research in patients suffering from dementia.

**Representation of dementia patients**

The discovery of effective interventions to prevent or delay disability in older persons is a public health priority. In order to let the growing number of dementia patients benefit from the findings in research, it is necessary that the results of the research trials can be extrapolated to the general population of dementia patients.

In the Netherlands, most people with advanced stages of dementia live in nursing homes, which is approximately 25% of all dementia patients. We have seen that the dementia research protocols mainly focus on mild/moderate dementia, as can be concluded from the MMSE/CDR scores used in the analysed protocols as well as by the requirement that people should still live at home. To be living independently at home, one would expect a MMSE score of approximately 15 or more. Most patients suffering from advanced dementia will not be living at home independently. When a patient is only eligible for enrolment in studies if living independently at home, it is safe to assume that he or she will not be suffering from advanced dementia. Dementia patients living in nursing homes differ in relevant aspects from patients living at home, concerning the severity of the dementia and the care needed. Many of the findings obtained in independently living patients cannot be extrapolated to severely demented patients. Since the severely demented patient group requires and receives the most intense care, one would expect a large proportion of the observational or care research to be conducted in this group.

The need for assistance with daily living, impaired cognition and incontinence can affect both the efficacy and the risks of a particular intervention and also the ability of a patient to implement a treatment or successfully complete self-management tasks.

Elderly patients typically have concomitance of multiple illnesses, as a result of two processes: the association between age and incidence of degenerative diseases and the development over time of complications of the existing diseases. Comorbidity is considered one of the hallmarks of geriatric patients, and a fundamental component of their complexity. Sensory impairment is prevalent among the elderly; in people aged 70 years or older, approximately 24% to 36% suffer from visual impairment or blindness and one-third of all people over the age of 65 experience disabling hearing loss. Somatic multimorbidity is prevalent in 35-98 patients aged 65 years or older. As shown in the results, most research protocols incorporate...
exclusion criteria regarding somatic comorbidities or sensory impairment. The research participants are generally required to be healthy and not sensory deprived, whereas the average dementia patient has several comorbidities, including sensory deficits. Therefore, dementia patients included in research protocols do not seem to represent the average patient population suffering from dementia. Excluding patients with comorbidities limits the external validity and might not truly represent the wider spectrum of patients seen in clinical practice. To the degree that it is clinically feasible, studies should include multimorbid individuals of all ages reflective of the general dementia population. A possible solution to the limited external validity of randomised controlled trials (RCTs) is the implementation of pragmatic studies (or real-life studies), which are gaining widespread recognition and support among clinicians and are of particular interest for policy-makers.²⁷,²⁹ Pragmatic studies are designed to evaluate the effectiveness of interventions in the full spectrum of real-life settings in order to maximise applicability and generalisability, as opposed to the optimal situations created in RCTs. Therefore, these studies are suitable for including a large number of participants, have a small number of eligibility criteria to allow a variety of patients in the trial, have patient-centred outcomes, and use clinical interventions similar to those used in routine care.²⁸,³³

A surprising finding that deserves attention is the frequent mention of ambiguous exclusion criteria. These criteria offer researchers too much freedom to selectively exclude potential research participants without the intervention of a Research Ethics Board. The selective exclusion of eligible research participants is, however, problematic for both scientific and ethical reasons. It results in an arbitrary selection of participants and limits both the internal and external validity of the study. Preventing eligible patients from participating in research is also known as gatekeeping,²⁸ and withholds the choice to participate from research participants.

Limitations
A limitation inherent to the use of the research registry includes missing data; for example the phase of the drug trial, information regarding the informed consent process and the competence of the research participant were not included in the publicly accessible part of the registry. Therefore, we could not provide a further analysis of the mismatch between the necessity for informed consent and the apparent lack of attention for the research participant’s competence. Furthermore, the registration of biomedical research trials in the web portal ToetsingOnline is a prospective register, the number of participants is based on an anticipation of the researchers and does not necessarily correspond with the actual number of enrolled participants.

Concluding remarks
In our study we found that the distribution of dementia research over the different types of dementia does not correspond with the prevalence of these dementia types in clinical practice. Furthermore, we found that the research population is not representative of the larger population of people suffering from dementia. Therefore, the possibility to extrapolate research findings of drug, intervention and observational studies to the patient population is limited. Furthermore, the exclusion of dementia patients in the more advanced stages of dementia in research studies means that this group of patients cannot benefit from possible therapeutic effects of the studies and may not profit from developed interventions and new insights, because this group differs significantly from the group of research participants. Moreover, ambiguously formulated exclusion criteria should always be avoided and should not be accepted by Research Ethics Boards, because these criteria limit the internal and external validity of the research.

A greater number of dementia patients could derive benefit from research if the research agenda were more closely aligned with disease prevalence. Lewy body dementia, familial dementia and vascular dementia are understudied compared with their disease prevalence and require more attention. In order to improve the generalisability of the research findings to the broader dementia population, it is important that the research participants reflect the population of patients. This is important for both intervention as well as observational studies. Regarding the extrapolation of research results of intervention studies, we encourage the conduct of ‘pragmatic studies’ in order to extend the applicability of RCT results to real-life settings. Our study may be useful to stakeholders, including policy makers, academic centres, industry, and investigators, and aid future decision-making regarding the conduct of trials in dementia patients. A better understanding of which conditions and populations are insufficiently addressed in the current research practice should provide guidance to organisations on how to allocate and prioritise available resources.

DISCLOSURES
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Early treatment with intravenous lipid emulsion in a potentially lethal hydroxychloroquine intoxication

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ABSTRACT

This case report describes the possible benefit of intravenous lipid emulsion in two patients surviving a severe intoxication with hydroxychloroquine in a dose that was previously considered to be lethal. The first case involves a 25-year-old female who ingested 17.5 grams of hydroxychloroquine, approximately one hour before presentation. An ECG showed QRS widening and the lab results showed hypokalaemia. She became unconscious, and developed hypotension and eventually apnoea. After intubation, supportive care consisted of norepinephrine and supplementation of potassium. Moreover, sodium bicarbonate and intravenous lipid emulsion were started to prevent cardiac toxicity. After these interventions, haemodynamic stability was established within a few hours. Although cardiomyopathy was confirmed, the patient recovered after two weeks. The second case concerns a 25-year-old male who took 5 grams of hydroxychloroquine. At presentation, two hours after intake, he showed QTc prolongation and hypokalaemia. The patient was treated with the usual supportive care and, although presentation to hospital was later, with intravenous lipid emulsion. Also this patient recovered. In conclusion, these cases show the benefit of supplemental intravenous lipid emulsion to prevent cardiac toxicity after a severe intoxication with hydroxychloroquine.

KEYWORDS

Lipid rescue, intoxication, hydroxychloroquine

INTRODUCTION

Hydroxychloroquine is well known for its antimalarial, antirheumatic and antilupus properties. Hydroxychloroquine poisoning is a rare but often fatal intoxication due to mainly cardiovascular toxicity. We present two patients who survived severe intoxication with hydroxychloroquine, in a dose that was previously considered to be lethal, using the usual supportive care and intravenous lipid emulsion.

CASE REPORT

The first case involves a 25-year-old female who ingested about 17.5 grams of hydroxychloroquine and about 550 mg diazepam in a suicide attempt, approximately one hour before presentation. An ECG showed QRS widening (figure 1). Abnormal lab results included a hypokalaemia of 2.7 mmol/l (table 1). After an initially agitated state, she became unconscious, and developed hypotension, vomiting and eventually apnoea. The patient was intubated and intravenous access was established to administer norepinephrine, which was titrated to aim for a mean arterial blood pressure above 65 mmHg. Diazepam was given in a dose of 2 mg/kg/24 hours and this therapy was continued during the following eight days. Intravenous lipid emulsion 20% was started in a bolus of 1.5 ml/kg (100 ml) followed by continuous infusion of 0.25 ml/kg/min (400 ml) for 30 minutes, in an attempt to decrease the uptake of the lipophilic hydroxychloroquine. To treat the decreased ventricular conduction, 100 ml of sodium bicarbonate 8.4% was also administered. A bolus of potassium chloride (40 mmol) was given to supplement the hypokalaemia. After these interventions, haemodynamic stability was established within a few hours. Retrospectively, hydroxychloroquine serum concentration measured using liquid chromatography-tandem mass spectrometry at admission was 5.5 µg/l. The hydroxychloroquine levels were measured several times in the next few days, showing a slow decline over time,
which can be explained by the large volume of distribution (figure 2). Two days after admission, the ECG showed a prolonged QTc interval (figure 2), and serum cardiac enzymes were elevated (table 1). Both normalised within a few days. Transoesophageal echocardiography showed an overall decreased function, confirming cardiomyopathy. The potassium levels remained stable throughout admission, and a cautious approach was taken towards supplementation of potassium. Due to pleural effusion and sedation, the patient was intubated for eight days. Two days later she was transferred to the psychiatric department for further treatment of her suicidal symptoms and borderline behaviour. The patient recovered without sequelae.

The second case concerned a 25-year-old male who ingested about 5 grams of hydroxychloroquine, 10 mg codeine and 10 mg domperidone. On presentation to the emergency department, two hours after intake, his symptoms consisted of vomiting, a QTc of 580 ms (figure 1) and a hypokalaemia of 2.7 mmol/l (table 1). Knowing the positive outcome of the first case, this patient was also treated with the same dose of intravenous lipid emulsion, diazepam 2 mg/kg/24 hours, a restrictive policy towards supplementation of potassium and alkalinisation of the blood using 100 ml of sodium bicarbonate 8.4%. The patient remained haemodynamically stable without signs of cardiomyopathy other than QTc prolongation. Therefore, vasopressor agents were not required. In the following days, the hydroxychloroquine levels and QTc gradually declined (figure 2). The patient recovered without sequelae.

**DISCUSSION**

Hydroxychloroquine poisoning is a rare but often fatal intoxication. Since 2012 several newspapers in the Netherlands and Belgium heeded the unlimited availability of hydroxychloroquine as a suicide pill. The fatal dose of hydroxychloroquine in humans has not been established. Death has been reported after intake of 5 grams, although survival after more than 20 gram has also been reported.\(^2\) In both presented independent cases, the hydroxychloroquine was ordered via an Internet Pharmacy in order to attempt suicide. Although the exact number of tablets taken cannot be ascertained, the measured blood levels suggest the intake of a significant number of tablets.

Hydroxychloroquine is rapidly absorbed, with peak concentrations within one to two hours after intake. It has a large volume of distribution and a long elimination half-life.\(^3\) Most deaths occur within three hours after intake, which is attributed to the transiently high blood concentrations of hydroxychloroquine due to almost complete and rapid absorption.\(^4\) Therefore, early treatment is essential for prevention of complications, even in the absence of symptoms.\(^5\) In the first case,

<table>
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<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
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<td>-</td>
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<td>82.5</td>
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<tr>
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</tbody>
</table>

ASAT = aspartate aminotransferase, CK = creatine kinase; CRP = C-reactive protein
treatment was initiated within one hour after intake of hydroxychloroquine. In the second case treatment was started two hours after intake. It seems that this early treatment was necessary to prevent a fatal outcome.

After absorption, the blood concentration decreases exponentially due to a high volume of distribution of 200 l/kg. Therefore, toxic symptoms will rarely last for longer than 24 hours even though the terminal elimination half-life is prolonged, approximately 45-60 days and even longer for its active metabolites. Whole blood concentrations of hydroxychloroquine are known to be about 4-8 times higher than serum concentrations. Blood concentrations of 2.5 µg/l and above are considered to be lethal. Due to the high volume of distribution, haemodialysis and haemoperfusion is not effective in hydroxychloroquine intoxication. The toxicity of hydroxychloroquine is primarily associated with cardiovascular complications. Hydroxychloroquine has sodium channel blocking properties and therefore, acting as a class Ia anti-arrhythmic drug, will slow down ventricular conduction resulting in ventricular arrhythmias. Cardiovascular collapse mainly occurs because of a negative inotropic effect, but peripheral vasodilation leading to hypotension and collapse also occurs. Hypokalaemia, due to increased intracellular distribution of potassium, may worsen the cardiac effects of hydroxychloroquine. Other symptoms that might occur in hydroxychloroquine overdose are respiratory arrest, convulsions, coma and vomiting. In our patients, all symptoms of hydroxychloroquine overdose were present, of which the cardiac symptoms were the most disturbing. The main focus of treatment lies in preventing haemodynamic complications. Currently, effective treatment to improve outcome of severe intoxication with hydroxychloroquine consists of the use of epinephrine, diazepam and mechanical ventilation. In case of acute respiratory distress syndrome or refractory circulatory shock, treatment with extracorporeal membrane oxygenation could be considered. The use of (nor)epinephrine is common practice in the treatment of hydroxychloroquine intoxication. It reverses the cardiotoxicity of hydroxychloroquine by vasoconstriction and reduces the intraventricular conduction time. Furthermore, the conduction disorder...
was treated through alkalisation of the blood with sodium bicarbonate, which is also known to be effective in treating QRS widening caused by quinidine-like substances. Several reports suggest that diazepam has an antiarrhythmic effect in hydroxychloroquine poisoning, although the mechanism behind this remains unclear. Possibly, this effect is related to both decreasing the sympathomimetic output in the central nervous system as well as stabilising the membrane of cardiac muscle by binding to specific receptors. The concomitant intake of diazepam in the first patient could have prevented her from developing severe cardiotoxicity. However, in patients with acute intoxication of 2 or more but less than 4 grams, diazepam did not appear to reverse the hydroxychloroquine-induced membrane-stabilising effect.

Most patients develop hypokalaemia due to increased intracellular distribution of potassium, which seems to have two opposite effects. A hypokalaemia may worsen pro-arrhythmic effects, but could also have a protective quality due to a compensatory mechanism tending to restore membrane excitability and inotropism by relative inhibition of the Na+/K+-ATPase pumps. Since hypokalaemia is not explained by depletion, correction of hypokalaemia should not be done aggressively, especially in the early hours.

Intravenous lipid emulsion has been used successfully in systemic anaesthetic toxicity and in poisoning with several other lipophilic drugs. The use of intravenous lipid emulsion is described in our hospital protocol in case of local anaesthetic toxicity. However, because of previous, sometimes fatal, intoxications with other lipophilic compounds (e.g. calcium channel blockers and beta-blockers) intravenous lipid emulsion is usually advised and used in case of intoxications with these compounds. Intravenous lipid emulsion seems to be a safe therapy with hardly any side effects and therefore it was used as treatment option in these two cases. The mechanism of action of intravenous lipid emulsion is poorly understood but it is believed to primarily prevent lipophilic substances from distributing to target tissues. Hydroxychloroquine is a highly lipophilic substance with a lipid/aqueous partition coefficient (log P) of 4.3 comparable with that of local anaesthetics, which makes intravenous lipid emulsion a possible effective treatment. However, the evidence for the use of intravenous lipid emulsion for hydroxychloroquine toxicity is limited and only a few case reports have been published, with no positive outcomes so far. In this case report, the immediate use of intravenous lipid emulsion, within one to two hours after intake of hydroxychloroquine, whether or not combined with diazepam, could have played a significant role in the patient’s survival. After administration of intravenous lipid emulsion, haemodynamic stability was achieved. After QTc prolongation was found, propofol and diazepam were started, in which propofol, as a lipid emulsion, could also have acted as an intravenous lipid emulsion.

Immediate, within one to two hours after intake of hydroxychloroquine, treatment with intravenous lipid emulsion, in combination with the usual supportive care known for poisoning with hydroxychloroquine (e.g. intubation, norepinephrine, diazepam and sodium bicarbonate), may have contributed to the survival of both patients.

Ten Broeke et al. Intravenous lipid emulsion in hydroxychloroquine intoxication.
CONCLUSION

Intoxications with hydroxychloroquine often result in a fatal outcome. Our observations have demonstrated that, besides the usual supportive treatment with norepinephrine, diazepam and mechanical ventilation, the early supplemental use of intravenous lipid emulsion might be a safe and effective treatment to prevent cardiac toxicity after possible lethal intoxication with hydroxychloroquine.

DISCLOSURES

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PHOTO QUIZ

Blue sclerae: diagnosis at a glance

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CASE

A 64-year-old Moroccan woman was referred to our outpatient clinic because of extreme fatigue. Her medical history revealed hypertension and femoral deep venous thrombosis (DVT). Furthermore, she had been using oral iron supplementation for anaemia due to iron deficiency for seven years. She suffered from occasional gastro-oesophageal reflux disease. Her stools were normal, without macroscopic blood, but black-coloured. She had no vaginal blood loss. Despite the fact that the DVT occurred two years earlier, she was still using oral anticoagulation. Her family history was unremarkable. Physical examination showed distinct blue sclerae with moderately pale conjunctivae. Abdominal and rectal examination revealed no abnormalities. Laboratory results demonstrated haemoglobin 4.8 mmol/l, mean cell volume 65 fl, ferritin 7 µg/l, transferrin saturation 3%, reticulocytes 40.8 x 10^9/l, normal levels of thrombocytes and leukocytes, haptoglobin, lactate dehydrogenase, vitamin B12 and folic acid. Renal and thyroid function was normal.

WHAT IS YOUR DIAGNOSIS?

See page 216 for the answer to this photo quiz.
DIAGNOSIS

A diagnosis of symptomatic microcytic anaemia was made. The origin of this anaemia could be multifactorial, but can be divided into iron deficiency, thalassaemia or anaemia of chronic disease. Occult blood loss in the gastrointestinal tract, provoked by oral anticoagulant use, was further investigated. Due to the use of oral iron supplementation, identification of melaena was difficult. First the anticoagulants and oral iron supplementation were stopped and both gastroscopy and colonoscopy performed. These showed no abnormalities, except a small submucosal lesion in the antrum, suspect for a gastro-intestinal stromal tumour. An oral iron-loading test showed reduced absorption of iron. Initially, thalassaemia could not be ruled out in the presence of severe iron deficiency. After abundant iron supplementation, the haemoglobin and mean cell volume normalised and haemoglobin electrophoresis was normal.

Ophthalmological evaluation by slit lamp showed mildly blue sclerae, but no further abnormalities. An additional ultrasound showed normal scleral thickness. It is unknown what the duration or severity of iron deficiency must be before blue sclerae develop. The mechanism is unclear, but it has been found that iron is an important cofactor in the hydroxylation of proline and lysine residues in collagen synthesis. In vitro tests showed that fibroblasts in culture do not synthesise collagen in the presence of iron-chelating agents. It is therefore hypothesised that collagen synthesis is impaired in patients with iron deficiency resulting in thin sclerae through which the choroid can be seen, making the sclerae appear blue. In our patient ultrasound of the sclerae showed normal thickness indicating that not only thickness, but also the consistency of the sclerae, may cause blue sclerae.

The association of blue sclerae and mucosal pallor with iron-deficiency anaemia was previously studied by Kalra et al. in 169 unselected hospital inpatients. Blue sclerae were seen significantly more often in patients with iron-deficiency anaemia (87%) than in those with other causes of anaemia (7%). The sensitivity of blue sclerae in patients with iron-deficiency anaemia was 87% with a specificity of 94%. By comparison, mucosal pallor was noted in only 30% of patients with iron-deficiency anaemia, with a sensitivity of only 20% and a specificity of 96% (p < 0.001). Concordance by three independent observers for blue sclerae was seen in 50.3% versus 56.8% for mucosal pallor in the studied patients. They reported that the presence of blue sclerae was unaffected by age, sex, colour of the iris, blood transfusions, skin thickness, pigmentation or perfusion.

Subsequent to this study in inpatients, the same investigators tested the predictive value of blue sclerae in undiagnosed chronic iron deficiency in apparently healthy individuals attending a general practice clinic. Of the 1889 patients screened, blue sclerae were observed in 41 patients. Of them, 34 (83%) had evidence of past or present iron deficiency. To date, more than one year after diagnosis, our patient is doing well and the haemoglobin and iron levels are within normal limits after repeated intravenous iron supplementation. However, the sclerae are still slightly bluish. It is unknown how long it takes to normalise sclerae composition after correction of iron levels. Kalra et al. reported that blue sclerae persisted in some patients, despite correction of the iron deficiency.

DISCUSSION

In general, one is triggered by pale conjunctivae to diagnose anaemia. This patient, however, had moderately pale conjunctivae as well as remarkable blue sclerae. The presence of blue sclerae is known to occur in osteogenesis imperfecta, inherited disorders of connective tissue and collagen disorders (e.g. Ehlers-Danlos syndrome, pseudoxanthoma elasticum) and long-term corticosteroid therapy.

However, a less known cause of blue sclerae is chronic iron deficiency. This association was first described by Osler in 1908 in iron-deficient undernourished teenage girls. Others reported the presence of blue sclerae in iron-deficient patients with other causes of iron shortage.

It is unknown what the duration or severity of iron deficiency must be before blue sclerae develop. The mechanism is unclear, but it has been found that iron is an important cofactor in the hydroxylation of proline and lysine residues in collagen synthesis. In vitro tests showed that fibroblasts in culture do not synthesise collagen in the presence of iron-chelating agents. It is therefore hypothesised that collagen synthesis is impaired in patients with iron deficiency resulting in thin sclerae through which the choroid can be seen, making the sclerae appear blue. In our patient ultrasound of the sclerae showed normal thickness indicating that not only thickness, but also the consistency of the sclerae, may cause blue sclerae.

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In conclusion, blue sclerae is an underestimated, often overlooked, but good indicator of iron deficiency and should become a regular part of clinical examination.

REFERENCES

PHOTO QUIZ

A butterfly in the belly: an unusual cause of intestinal obstruction

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CASE REPORT

A 52-year-old man presented with a three-week history of abdominal pain, nausea and vomiting. His HIV-1 infection was successfully suppressed with antiretroviral therapy and in 2005 he was treated for pulmonary tuberculosis. At presentation in the emergency department he was haemodynamically stable and physical examination showed no abnormalities. Laboratory results revealed mild signs of dehydration (blood urea nitrogen 7.9 mmol/l, creatinine 107 μmol/l, haematocrit 0.50 l/l) without signs of inflammation (C-reactive protein 3 mg/l). Abdominal ultrasound revealed multiple thickened, irregular small bowel loops. He was admitted to the internal medicine ward for rehydration and further evaluation. Because of persistent vomiting, a gastroduodenoscopy was performed. Stomach retention (without further abnormalities) was present despite the fact that the patient did not have any oral intake prior to the procedure. A CT scan of the abdomen showed a dilated stomach and duodenum.

Figure 1. Coronal CT image shows a cluster of proximal jejunum loops in the left upper quadrant (arrowheads). The stomach and duodenum were dilated (duodenum was 4.2 cm wide) and obstructed at the level of the ligament of Treitz (arrow). The proximal jejunal loops were surrounded by a small band-like structure.

Figure 2. Axial CT image displays an encapsulated proximal jejunum in the left upper quadrant of the abdomen. A fibro-collagenous, non-calcified membrane was identified surrounding a cluster of proximal jejunal loops (arrowheads).
up to 4.2 cm. There was a calibre change at the Treitz ligament with a subtotal obstruction of the jejunum. Furthermore, a fibro-collagenous, non-calcified membrane was surrounding a cluster of proximal jejunal loops (figure 1 and 2). In addition, a diagnostic laparoscopy was performed (figure 3).

WHAT IS YOUR DIAGNOSIS?

See page 220 for the answer to this photo quiz.
DIAGNOSIS

Laparoscopy revealed a circa 75 cm long, white layer starting at the Treitz ligament covering the proximal jejunum and peritoneum. Extensive adhesiolysis was performed. After the surgical procedure, the patient quickly recovered. Biopsies were taken and pathological examination showed fibro-adipose tissue with minimal non-specific signs of chronic inflammation.

Encapsulating peritoneal sclerosis (EPS) is a rare clinical condition in which chronic inflammation leads to formation of a fibrocollagenous, cocoon-like membrane that can partially or totally encase the small bowel. As the formation of this membrane causes adhesions, intestinal obstruction can occur and patients typically present with nausea, vomiting, abdominal pain, abdominal distention or constipation. The duration of symptoms can vary between a few days up to 18 years depending on the severity of the obstruction.

As preoperative diagnosis is difficult, EPS is frequently diagnosed during surgical procedures.

Treatment of EPS is predominantly surgical although this is not always necessary in asymptomatic EPS.

Primary or idiopathic EPS was first named ‘abdominal cocoon syndrome’ by Foo in a case series of ten adolescent women. The aetiology of primary EPS remains unclear. In secondary EPS, which is more common than primary EPS, local or systemic factors lead to inflammation in the peritoneum. Although the exact pathophysiology of secondary EPS is not fully understood, it has frequently been reported in peritoneal dialysis patients and in patients with peritoneal tuberculosis. As our patient had received successful treatment for pulmonary tuberculosis in the past and laparoscopy revealed no characteristic signs of abdominal tuberculosis (e.g., mesenteric abscesses, enlarged lymph nodes, tubercles over the bowel serosa), it is unlikely that this caused the formation of EPS.

In summary, EPS is an uncommon cause of complete or incomplete bowel obstruction resulting from an idiopathic or inflammatory reaction in the abdomen. Diagnosing EPS is challenging as both clinical and radiological signs are rather non-specific. When symptomatic, surgical adhesiolysis with membrane resection is the treatment of choice.

CONCLUSION

Encapsulating peritoneal sclerosis (EPS) / abdominal cocoon syndrome.

REFERENCES

PHOTO QUIZ

A 49-year-old woman presenting with aphasia

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CASE REPORT

A 49-year-old woman presented to the Emergency Department with aphasia; the time of onset was unknown. Her past medical history revealed a syphilis infection in 1987 and alcohol abuse. On neurological examination she spoke mainly non-existent words, her comprehension was relatively unaffected. Furthermore, there was a mild right-sided central facial palsy, right-sided hyperreflexia, and bilateral Babinski signs. Computed tomographic imaging of the brain showed a hypodense lesion in the left hemisphere. Magnetic resonance imaging of the brain revealed hyperintense, confluent grey matter and white matter lesions in the left hemisphere (figure 1). The lesions were isointense on T1 weighted images and enhanced after administration of gadolinium.

WHAT IS YOUR DIAGNOSIS?

See page 222 for the answer to this photo quiz.

Figure 1. MRI images of the brain
Panel A: Axial FLAIR image showing hyperintense, confluent grey matter and white matter lesions in the region of the left middle cerebral artery
Panel B: Axial diffusion weighted image showing diffusion restriction around the left middle cerebral artery
Panel C: T1 axial image after administration of gadolinium showing enhancement of the lesions
Panel D: Axial T2 image two months later showing a reduced degree of enhancement after administration of gadolinium
DIAGNOSIS

Her past medical history revealed a syphilitic infection in 1987. In 2010, when a lumbar puncture was needed to rule out neurosyphilis, she withdrew herself from medical control. *Treponema pallidum* haemagglutination assay (TPHA) in serum was grossly reactive (1:10,240), while rapid plasma reagin (RPR) was not reactive (1:1). A lumbar puncture was performed and cerebrospinal fluid (CSF) analysis showed an elevated protein of 1.27 g/l, a slightly raised cell count of 8 x 10⁶/l and a glucose level of 3.4 mmol/l. The TPHA was increased (1:16) in the CSF, but RPR was negative. A HIV test was negative. Because of the presence of a recent infarction in the distribution of the left middle cerebral artery on MRI imaging of the brain, the diagnosis neurosyphilis of the meningovascular type was made.¹² The patient was treated with intravenous benzylpenicillin, but substantial aphasia persisted. Two months later follow-up MRI of the brain revealed the same grey matter and white matter lesions, with a reduced degree of enhancement after administration of gadolinium (figure 1D) and the aphasia had improved.

Neurosyphilis is an infection of the central nervous system caused by *Treponema pallidum* and can occur at any time in the course of the infection.¹ There are four different types of symptomatic neurosyphilis: tabes dorsalis, dementia paralytica, syphilitic meningitis and meningovascular syphilis. In case of neurological symptoms in a patient with a medical history of a syphilitic infection, neurosyphilis should be considered. In CSF, the RPR has a high false-negative rate and also TPHA can be negative in case of tertiary syphilis.¹³ In these cases, the main diagnostic criteria are protein level and cell count in CSF. Treatment of neurosyphilis consists of intravenous administration of benzylpenicillin 18 to 24 million units a day for 10-14 days. During follow-up a lumbar puncture should be repeated every six months until the protein level and cell count have normalised.⁴ In general, comparable to our patient’s situation, patients with meningovascular syphilis do not always recover completely.

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REFERENCES

PHOTO QUIZ

A crystal clear diagnosis

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CASE REPORT

A 72-year-old male with type II diabetes, complaining of pain in his left arm, was prescribed oral valacyclovir for two weeks because of suspected local herpes zoster infection. Afterwards, the patient was admitted to the neurology ward with nausea and vertigo, with the differential diagnosis including herpes encephalitis; treatment with intravenous acyclovir 700 mg three times a day was started. After polymerase chain reaction testing of the cerebrospinal fluid was found to be negative for herpes viruses, and the acyclovir treatment was discontinued after three doses.

However, one day later, during routine control of his renal function, the estimated glomerular filtration rate had decreased from 76 to 14 ml/min/1.73 m², even after fluid repletion. The serum potassium was 6.3 mmol/l. During admission there had been no period of hypovolaemia; an ultrasound excluded postrenal obstruction. Urine analysis by polarised microscopy revealed needle-shaped crystals (figure 1).

WHAT IS YOUR DIAGNOSIS?

See page 224 for the answer to this photo quiz.
DIAGNOSIS

The diagnosis of acute crystal-induced kidney insufficiency by acyclovir was established by birefringent microscopy, which showed typical needle-shaped crystals. It is well known that different kinds of medication can cause crystal-induced kidney damage, due to intratubular precipitation of crystals which results in obstruction. Acyclovir, but also amoxicillin, sulphonamide antibiotics, ciprofloxacin, indinavir, triamterene and methotrexate, are known to cause crystal-induced kidney damage. In the case of acyclovir, apart from crystal-induced acute kidney insufficiency, also direct tubular damage might be responsible for the loss of renal function. The clinical course of crystal-induced kidney insufficiency is characterised by a rapid rise of serum creatinine within the first 12-48 hours after initiation of treatment. Apart from dose, volume depletion is a major risk factor. Patients are often asymptomatic although they may have flank pain. Urine analysis shows crystals and sometimes microscopic haematuria.

The gold standard for the diagnosis of crystal-induced renal failure is kidney biopsy. However, in most cases the disease is self-limiting and a biopsy is often not indicated. Diagnosis then relies on urine sediment revealing the characteristic crystals. In some cases temporary haemodialysis is necessary. Crystal-induced kidney failure should always be considered in the differential diagnosis of acute renal failure. It can be detected by polarised light microscopy of the urine sediment. Because renal function improves with fluid suppletion in most cases, haemodialysis is rarely necessary.

REFERENCES


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Full-dose sofosbuvir and daclatasvir for chronic hepatitis C infection in haemodialysis patients

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To the Editor,

The registration of sofosbuvir-containing regimens has changed the treatment of hepatitis C virus (HCV) infection dramatically by achieving high sustained virological responses (SVR).1-3 Even previously difficult-to-treat patients can now be treated safely by interferon-free therapies, resulting in potential reduction of HCV disease burden in the Netherlands.4-5 However, treating patients with end-stage renal disease (ESRD) remains difficult. Currently approved options for ESRD patients still contain (pegylated) interferon as a backbone, which is historically associated with low SVR rates and high side effect profiles.6-8 Since HCV infection negatively impacts morbidity and mortality compared with non-HCV dialysis patients, effective treatment is especially pivotal for this patient group.9 In addition, clearance of HCV will increase the chance of getting a renal transplant, as HCV-infected individuals demonstrate higher mortality, graft loss rate and episodes of rejection after renal transplantation.10 Therefore, there is a clear need to treat haemodialysis patients with interferon-free therapies. The recommended dose of 400 mg sofosbuvir in patients without renal insufficiency is not approved for patients on haemodialysis owing to concerns of accumulating metabolites with potential cardiovascular and hepatobiliary toxicity.11 Indeed, sofosbuvir is metabolised to the active metabolite GS461203 which works intracellularly, and subsequently to the inactive metabolite GS331007, which is the predominant metabolite in plasma.12 Because GS331007 is eliminated by the kidney, concern was raised that especially this metabolite would accumulate in patients on haemodialysis, potentially leading to toxicity.13 Lowering the dose is not a desirable option, as sofosbuvir is a prodrug and potentially could lead to lower levels of the active metabolite GS461203 and lower efficacy. Indeed, a small study in ten genotype 1 HCV infected patients with a creatinine clearance < 30 ml/min using sofosbuvir 200 mg daily showed low efficacy (SVR 40%).14 These findings suggest that standard doses of sofosbuvir 400 mg might be necessary to achieve SVR in haemodialysis patients, but the tolerability is unknown.

We treated two HCV genotype 1 patients with standard dose sofosbuvir (400 mg) and daclatasvir (60 mg) once daily for 12 weeks. Both patients were on haemodialysis at the start of anti-viral treatment. The aetiology of ESRD was reflux nephropathy and diabetic nephropathy for patient A and B respectively.

Patient A (male, 54 years) had treatment-naïve chronic HCV genotype 1b with Child-Pugh A cirrhosis, and started with a regimen consisting of sofosbuvir/daclatasvir/ribavirin. Ribavirin was dosed at 200 mg daily after an initial loading dose of 1200 mg for the first two days, and was subsequently adjusted based on weekly measured ribavirin levels. The pre-treatment HCV RNA level was 72,000 IU/ml, dropped to undetectable at week 4, and remained undetectable until 12 weeks after treatment (SVR). Due to persistent anaemia after lowering the ribavirin dose, the ribavirin was stopped at week 5. No other adverse events occurred. One of the reasons that patient A refused a transplant (after already having two renal transplant rejections) was fear of HCV. After successful treatment, he is now reconsidering transplantation.

Patient B (female, 63 years), who had chronic HCV genotype 1a with Child-Pugh A cirrhosis, and started with a regimen consisting of sofosbuvir/daclatasvir/ribavirin. Ribavirin was dosed at 200 mg daily after an initial loading dose of 1200 mg for the first two days, and was subsequently adjusted based on weekly measured ribavirin levels. The pre-treatment HCV RNA level was 72,000 IU/ml, dropped to undetectable at week 4, and remained undetectable until 12 weeks after treatment (SVR). Due to persistent anaemia after lowering the ribavirin dose, the ribavirin was stopped at week 5. No other adverse events occurred. One of the reasons that patient A refused a transplant (after already having two renal transplant rejections) was fear of HCV. After successful treatment, he is now reconsidering transplantation.

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improved after finishing therapy. She is now in the screening process for receiving a renal transplantation. Both patients achieved SVR12 after receiving full-dose sofosbuvir, and tolerated treatment well. We did not observe any evidence of hepatobiliary (1.5 fold elevation of aminotransferase or alkaline phosphatase level) or cardiovascular toxicity (occurrence of myocardial infarction/angina/arrhythmia) during treatment. Only patient A reported anaemia, which resolved after cessation of ribavirin.

We are the first to report that the interferon-free sofosbuvir-based regimen including daclatasvir is effective and tolerated well in cirrhotic HCV genotype 1 patients on haemodialysis. Our results are in line with three recent case series that investigated other sofosbuvir-containing regimens in HCV genotype 1 patients with ESRD. All three case series used 400 mg sofosbuvir with simeprevir or ledipasvir and reported good safety profiles and superior SVR when compared with SVR’s (< 60%) of interferon-based therapies. Moreover, most studies used a ribavirin-free regimen. Given the risk of worsening of pre-existent anaemia when using ribavirin (see patient A) and the superior SVR observed in aforementioned trials, the use of sofosbuvir without ribavirin would be a viable option in this specific population. On the other hand, European Association for the Study of the Liver (EASL) guidelines recommend the use of ribavirin in patients with cirrhosis, where possible. The low number of patients in this and other studies remains a limiting factor for definite conclusions. When ribavirin is used, we recommend therapeutic drug monitoring to prevent concentration-related anaemia by overdosing of ribavirin in this group of HCV patients with renal impairment.

The Dutch HCV guideline committee (http://www.richtsnoer.nl/index.html) advises to use full-dose sofosbuvir in HCV patients with ESRD (if treatment is warranted), as lowering the dose increases the chance for virological failure more than the risk for toxicity when using a standard dose. The low side effect profiles mentioned in our letter and observed in recent studies support this statement.

Previous studies showed that only 18% of GS331007 is removed by a four-hour haemodialysis session, indicating that these patients are exposed to higher levels of this inactive metabolite compared with subjects with normal renal function. Given the low side effect profiles reported in the aforementioned studies, and the fact that the cardiovascular and hepatobiliary toxicity was only observed in premarket animal studies, it remains the question whether this metabolite is really toxic for ESRD patients for the duration of 12-24 weeks of treatment. Unfortunately, we did not measure levels of sofosbuvir or GS331007 in these two patients. Further pharmacokinetic/dynamic studies are necessary to unravel the potential toxicity of sofosbuvir and its metabolites in patients with ESRD.

The use of sofosbuvir-containing regimens in haemodialysis patients may be short-lived. New regimens that are completely metabolised by the liver are close at hand. The combination of grazoprevir combined with elbasvir for HCV genotype 1 infected patients with ESRD has recently been approved by the US Food and Drug Administration (FDA), as well as the combination ombitasvir/paritaprevir/ritonavir with or without dasabuvir, given the excellent preliminary results. However, these combinations will be contraindicated in patients with Child-Pugh C (grazoprevir) or decompensated Child-Pugh B/C cirrhosis (ombitasvir/paritaprevir/ritonavir). Since a large proportion of patients with advanced cirrhosis will have ESRD, sofosbuvir-containing regimens remain a relevant therapeutic option for HCV patients on haemodialysis.

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