A combination of nodes: what is your diagnosis?

POTS: a common, yet unfamiliar syndrome

Hepatitis B screening before chemotherapy

Radiation-induced morphea: autoimmunity as a risk factor

Unexplained behavior and decreased level of consciousness
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C3 glomerulopathy, a new but still evolving entity

S.A.M.E.G. Timmermans, P. van Paassen*

Department of Nephrology and Clinical Immunology, Maastricht University Medical Center, Maastricht, the Netherlands. *Corresponding author: p.vanpaassen@maastrichtuniversity.nl

Ever since the clinical introduction of kidney pathology in the mid-1950s, new entities have been introduced into the spectrum of diverse glomerulopathies. Kidney pathology relies on light, immunofluorescence and electron microscopy. Although classification of glomerulopathies for many years has been based on morphology (i.e., the pattern of injury), we currently diagnose patients according to the cause of injury, as identical “patterns” can be linked to distinct mechanisms and thus, targets for treatment. C3 glomerulopathy (C3G), for example, has been introduced to detect patients with defects in complement activation as the cause of glomerulonephritis (GN). C3G is a rare disease found in ~2% of native kidney biopsies annually in the Netherlands (Limburg Renal Registry, unpublished data). Complement defects can be caused by circulating factors, such as (monoclonal) immunoglobulins and/or rare variants in complement genes encoding proteins that either regulate or activate complement, leading to accumulation of C3 fragments and variable glomerular inflammation. In the past, however, many of these patients have been diagnosed with idiopathic proliferative GN, neglecting the crucial role of complement. At present, various complement therapeutics, some with potential efficacy for C3G, are being investigated, making the correct recognition of C3G relevant.

In this issue of The Netherlands Journal of Medicine, Koopman and colleagues provide an overview of diagnosis and treatment of C3G. Patients who fulfill the pathologic criteria for C3G, that is, a proliferative GN with dominant staining for C3, either with subtle or no Igs, should be screened for defects in complement regulation. C3 nephritic factor (C3Nef) and, to a lesser extent, factor H autoantibodies (FHAA) can be found in > 50% of patients, enhancing C3 activation and the accumulation of C3 fragments in glomeruli. Igs that interfere with other factors are emerging, although rare. In addition, rare variants in complement genes can be found in ~20% patients and, in particular, among familial cases. The interpretation of the genetics of C3G, however, is complex and more research is needed to gain insight into genotype-phenotype correlations; the Database of Complement Gene Variants (http://www.complement-db.org) provides an excellent overview of our current understanding.

The prognosis of C3G varies from clinical remission to end-stage renal disease in ~40% and >10% of patients, respectively. Koopman and colleagues correctly state that no treatment has been proven effective for C3G, although mycophenolate mofetil may protect against disease progression, particularly among patients with C3Nef and/or FHAA serum reactivity. Immunosuppression should therefore be used in patients with “autoimmunity” or in those with a rapid decline in renal function. C3G, by definition, indicates a complement defect, providing a rationale for complement therapeutics. Eculizumab, a potent C5 inhibitor and, to date, the sole commercially available agent, only showed benefit for patients with C3G presenting with vasculitis-like lesions, that is, crescentic GN, on kidney biopsy. Importantly, C3G is caused by activation of C3 upstream of C5 that is not affected by eculizumab. The benefit for patients with “crescentic” C3G may reflect blockade of C5a (i.e., the activation product of C5 and a potent anaphylatoxin), thereby reducing glomerular inflammation, a mechanism that has been proven effective in the anti-neutrophil cytoplasmic antibodies-associated vasculitides. It appears, however, not to prevent the accumulation of C3 fragments within the glomeruli. New therapeutics that specifically target the process of C3 activation, such as factor D inhibitors, are now being studied in phase II clinical trials (e.g., NCT03369236, NCT03459443). It is important to note that most of the published C3G cohorts represent a mixture of distinct underlying causes, some of which may be linked to monoclonal Igs and/or masked Igs. The high prevalence of monoclonal Igs (often classified as monoclonal gammopathies of renal significance) in adult C3G and the induction of a favorable renal response upon clone-directed treatment suggests a causal link. Apparently, monoclonal Igs in these cases
enhance C3 activation and thereby progression of C3G. Patients with progressive renal disease may therefore benefit from clone-directed treatment,\textsuperscript{7,8} whereas treatment may be postponed among those with low-grade proteinuria and no evidence of progression.\textsuperscript{9} At present, diagnostic tests that prove the mechanistic link between the monoclonal Igs and complement dysregulation are needed to better select patients for clone-directed treatment.

Moreover, a small subset of patients with C3G may present with false-negative staining for Igs on frozen tissue sections using routine immunofluorescence microscopy;\textsuperscript{10} these so called “masked” Igs also can be found in patients with mixed essential cryoglobulinemia or in isolation with no gammopathy. Positive staining for C4d on kidney biopsy indicates the presence of Igs, favoring immunosuppression. It remains to be proven whether complement therapeutics are effective for the treatment of these specific cases.

Taken together, C3G is an important new entity in the diagnostic field of kidney pathology. Better understanding of its etiology and pathogenesis is needed to develop targeted treatment modalities and improve patient care. Koopman and colleagues illustrate the importance of individualized decisions regarding treatment for patients with C3G.\textsuperscript{2} The fast evolution of complement therapeutics is promising and may shift the paradigm of treatment towards the targeted approach that makes so much more sense.

REFERENCES

Postural orthostatic tachycardia syndrome (POTS): a common but unfamiliar syndrome

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Departments of \textsuperscript{1}Internal Medicine, \textsuperscript{3}Clinical Genetics, Erasmus University Medical Center, Rotterdam, the Netherlands; \textsuperscript{2}Department of Cardiology, Franciscus Hospital, Rotterdam, the Netherlands; \textsuperscript{4}Department of Internal Medicine, Radboud University Medical Center, Nijmegen, the Netherlands. *Corresponding author: j.versmissen@erasusmc.nl

ABSTRACT
Postural orthostatic tachycardia syndrome (POTS) is a condition in which a change from a supine to an upright position causes an abnormally large increase in heart rate which may be accompanied by a variety of physical complaints. We report two cases illustrating the heterogeneity of this syndrome. We give an update on the etiology of POTS, which is still poorly understood, and its overlap with other syndromes such as chronic fatigue syndrome. Clinicians should be aware of POTS, a fairly common clinical entity, that can result in significant impairments to a patient’s quality of life. Lifestyle measures (under which adequate fluid and salt intake, exercise) are a first line of treatment; if insufficient, pharmacotherapy can be considered to improve quality of life.

KEY WORDS
Postural orthostatic tachycardia syndrome, orthostatic intolerance

INTRODUCTION
Postural orthostatic tachycardia syndrome (POTS) is a condition in which a change from a supine to an upright position causes an abnormally large increase in heart rate.\textsuperscript{1} A POTS diagnosis is made when patients meet all criteria shown in table 1. Common complaints, not all explained by the increase in heart rate only, are lightheadedness, palpitations, (pre-)syncope, fatigue, tremulousness and weakness or heaviness (especially of the legs).\textsuperscript{2,3} POTS is probably underdiagnosed due to the heterogeneity in both presentation and etiology, and therefore the prevalence of POTS is still unsure. Three studies report a prevalence of approximately 170/100,000 in the United States.\textsuperscript{4-6} Mean age of onset of POTS is approximately 30 years and most patients are between the ages of 20-40 years. There is a clear overrepresentation of women with a corresponding female: male ratio of 5:1.\textsuperscript{6} We describe two illustrative cases, followed by considerations regarding pathophysiology and treatment consisting of lifestyle advice. This advice may include psychological interventions which, if necessary, may be combined with pharmacotherapy.

CASE REPORTS
Case 1
A 24-year-old Caucasian woman with an unremarkable medical history was referred to the outpatient clinic of internal medicine. Her referring cardiologist suspected POTS based on complaints of vertigo and postural-dependent sinus tachycardia; the patient had no severe orthostatic hypotension and a structurally normal heart as

<table>
<thead>
<tr>
<th>Table 1. Criteria for the postural orthostatic tachycardia syndrome \textsuperscript{1,6}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate increases \geq 30 (40 in children 12-19 years) bpm from supine to standing (10 minutes)</td>
</tr>
<tr>
<td>Symptoms worsen with standing and improve with recumbence</td>
</tr>
<tr>
<td>Symptoms last \geq 6 months</td>
</tr>
<tr>
<td>Absence of orthostatic hypotension (\geq 20 mmHg drop in systolic blood pressure)</td>
</tr>
<tr>
<td>Absence of other overt cause of orthostatic symptoms or tachycardia</td>
</tr>
</tbody>
</table>

Bpm = beats per minute
imaged by echocardiography. Her complaints, which also included flushing, malaise and concentration problems, started approximately three months earlier and improved when lying down and worsened when standing. Her sister and father had similar symptoms at the same age.

We performed a tilt table test. Her supine blood pressure was 141/84 mmHg and her heart rate was 111 beats per minute (bpm). After being tilted, physical complaints such as flushing and palpitations developed progressively and after seven minutes, the test was stopped. Her heart rate rose to 150 bpm while blood pressure increased slightly to 148/96 mmHg. At this point, blood tests were conducted. Serum noradrenaline level was 887 pg/ml (baseline 292 pg/ml) and adrenaline level was 509 pg/ml (baseline 44 pg/ml). These complaints and findings, in absence of another explanation such as adrenal insufficiency, confirmed the diagnosis of POTS (Table 1). Since she had such a severe rise in heart rate and two first-degree relatives had similar symptoms, whole exome sequencing was performed after pretest counseling. No pathogenic variant, not even in the SLC6A2 gene (a gene that causes orthostatic intolerance), was identified.

We advised lifestyle changes, including substantial fluid and salt intake, compression stockings and supervised physical reconditioning (horizontally; for example, cycling). Simultaneously, as part of the recommended dual policy of physical and psychological treatment, we referred her to a psychologist to discuss psychological factors that could contribute to her POTS symptoms.

As her symptoms did not improve within weeks, we prescribed short-acting beta blocker propranolol (up titrated to 40 mg three times a day) and fludrocortisone (62.5 mcg once daily), combined with extra salt (NaCl tablets, 1000 mg three times a day). This resulted in good response, but the fludrocortisone led to severe insomnia. The patient herself suggested modafinil (100 mg bidaily) after reading Raj et al., which was prescribed for her difficulty with concentration. This improved her so-called “brain fog”.

For exceptional occasions such as her wedding, she was prescribed desmopressin (DDAVP) after a test-dose including control of sodium levels was conducted, which improved her symptoms substantially. Over time, and considering all lifestyle measures, her condition improved and medication could be tapered after six months to propranolol 40 mg three times a day and salt suppletion only. Currently, her symptoms are well under control with propranolol 40 mg three times a day and salt suppletion.

Case 2

A 44-year-old Caucasian male visited the general practitioner with complaints of syncope while standing. These complaints were present for approximately five to six months and started after an intentional weight reduction of 30 kg (weight at presentation: 95 kg, height: 1.97 m). Simultaneously, he developed paresthesia of his legs. He was referred to an internist and a cardiologist for further investigation. The cardiologist excluded underlying cardiac pathology. The internist referred him to our hospital for further diagnostics, in particular, a tilt table test. This was performed, and showed an increase in heart rate from 58 bpm in supine position to 90 bpm when tilted, whereas his blood pressure remained around 154/98 mmHg. Noradrenaline rose to 229 pg/ml from a relatively low baseline level of 69 pg/ml. These measurements fit the criteria of POTS (Table 1).

The neurologist we consulted in our center concluded the paresthesia to be meralgia paresthetica of the right femoral cutaneous nerve and the left peroneal nerve, possibly triggered by the patient’s weight loss. An association with POTS was excluded, although no biopsy was performed to rule out small fiber neuropathy. We advised lifestyle changes, including intake of sufficient fluids and salts and prescribed sodium (NaCl tablets, 1000 mg three times a day). The symptoms of the patient resolved and no further pharmacotherapy was required.

DISCUSSION

This paper describes two illustrative cases of patients with POTS. POTS, first described by Jacob Mendes Da Costa in 1871, is a clinical syndrome and not a distinct disease entity, and has clinical overlap with chronic fatigue syndrome and Ehlers-Danlos syndrome. Clinical diagnostic criteria for POTS are provided in Table 1.

Pathophysiology

Under normal circumstances, heart rate and blood pressure remain stable or change only slightly and for a very short period of time in response to changing from a supine to an upright position due to a rapid response originating from the baroreceptors. In POTS patients however, heart rate increases to very high levels and for a longer time period. This is presumably due to different pathways. Hypovolemia is present in two-third of patients with POTS, potentially due to less responsiveness of the renin–angiotensin–aldosterone system. Elevated (> 600 pg/ml) catecholamine levels upon standing are commonly recognized in patients with POTS. Poor exercise tolerance and deconditioning is also present in the majority of cases. Although this could be a cause or a consequence of POTS, the fact that most patients benefit from exercise is an extra argument that deconditioning is a causal factor. In addition to these common findings, two specific subtypes can be distinguished in most studies: the hyperadrenergic and the neuropathic subtypes, although in clinical practice this subdivision is less useful and difficult to differentiate. A vast majority of POTS patients...
experience autonomic dysfunction in various autonomic domains. Additional testing, such as measurement of catecholamines in response to standing or assessment of small fiber neuropathy, should be preserved for research purposes only or in specific indications—such as in case 2, where a relationship with the tremendous weight loss was likely.

Hyperadrenergic phenotype

A hyperadrenergic state, present in approximately 50% of patients with POTS, is due to excessive sympathetic discharge characterized by a supraphysiological rise in plasma levels of noradrenaline to 600 pg/ml or higher in response to standing as seen in case 1. Blood pressure may fluctuate or increase heavily (“orthostatic hypertension”) during prolonged standing. Symptoms of stress, emotional behavior and cold pale skin may occur upon standing. Likewise, the episodes can also be triggered by emotional stimuli and physical activity. Earlier described hypovolemia may also attribute to the hyperadrenergic state. Hyperthyroidism or catecholamine-secreting tumors should be ruled out as alternative diagnoses in patients presenting with this phenotype. In rare cases of familiar occurrence of POTS, a heterozygous variant in the SLC6A2 gene encoding the norepinephrine transporter has been found.

Hyperadrenergic states have also been suggested to be secondary to immune disorders associated with antibodies against components of the voltage-gated potassium channel complex. Autoantibodies against the nicotinic acetylcholine receptor have been described to correlate with the severity of autonomic dysfunction in small patient cohorts. Recent studies have shown elevated autoantibodies against adrenergic receptors (α1AR) in patients with POTS, resulting in a compensatory autonomic vasoconstriction and concurrent α1AR-mediated tachycardia. Furthermore, another study showed Angiotensin II Type 1 Receptor autoantibodies (AT1R) in POTS patients. However, these are small studies in selected patient populations and therefore further research is needed to establish the clinical implications.

Neuropathic phenotype

The other important mechanism found in POTS is presumably caused by (partial) peripheral sympathetic denervation leading to impaired peripheral vasoconstriction. This denervation is thought to be a consequence of a small fiber neuropathy, which may be diagnosed by biopsy, impaired sweat testing or sudomotor axon reflex testing. There is lack of vasoconstriction resulting in venous pooling in the lower limbs, which is reversed when the patient lies down as a result of gravity. Considering these aspects, the second case is expected to have the neuropathic form of POTS potentially related to his weight loss although biopsy was not performed. Indeed, in a small study over one third of patients fulfilled the criteria for POTS after bariatric surgery.

Diagnostic approach

POTS patients present with atypical and rather common symptoms. The diagnostic approach is therefore challenging and based on four criteria (table 1) while excluding other causes (table 2). A key symptom for establishing the diagnosis of POTS within the differential diagnosis is worsening of symptoms while standing up. Since epidemiology and symptoms may overlap, inappropriate sinus tachycardia and vasovagal syncope must be distinguished from POTS, although these diagnoses are not mutually exclusive. Any condition or drug that could be causing orthostatic tachycardia, such as dehydration or pheochromocytoma, should be identified and adequately treated. The tilt table test is commonly used for diagnosing POTS, although this is not strictly necessary: a simple stand test might be sufficient to confirm the diagnosis; the same is true for the measurement of catecholamines before and after tilting.

Overlap with other conditions

There seems to be an overlap with fibromyalgia (FM) and other medically unexplained physical symptoms (e.g., chronic fatigue sleep disturbances). POTS is found in up to 50% and 60% of patients with chronic fatigue syndrome (CFS) and FM, respectively. In patients with CFS, abnormalities of the vascular and autonomic nervous system are common. Similar to POTS patients, small fiber neuropathy also affects a majority of FM patients. Given the similarities between symptoms of FM, CFS and POTS, it is reasonable to assume shared etiology between these conditions. This may involve so-called “somatic hypervigilance” or “central sensitization,” in which relatively mild or routine sensory information is experienced more intensely or more distressing than usual. This may also lead to a stronger physiological response to exercise, often reason to quit exercising.

Treatment options

Currently, there is no standard treatment for POTS, and treatment strategies should be based on clinical presentation, the assumed underlying pathophysiology, potential overlapping syndromes, deconditioning and any psychological factors that can sustain symptoms. First-line POTS therapy consists of lifestyle recommendations. A multidisciplinary approach including physiotherapy and psychological support is recommended to optimize lifestyle treatment to avoid overmedicalization.
Since hypovolemia seems to play a major role in the majority of patients, fluid intake of at least 2-3 liters as well as 10 grams of salt per day (studies differ in their advice between 8-10 or 10-12 grams) should be advised to prevent hypovolemia. A 24-hour urine measurement of sodium can be helpful since most patients often overestimate their current salt intake. Most patients may benefit from wearing support garments such as thigh- or waist-high tight support stockings in accordance with recommendations for orthostatic hypotension. Patients should be encouraged to begin a gradual program of physical reconditioning under supervision of a dedicated physical therapist, working toward a goal of performing 20 to 30 minutes of aerobic activity (preferably horizontal, e.g., cycling) three times a week.

Psychological treatment including psychotherapy can be helpful, both to improve coping mechanisms as well as to address the somatic hypervigilance. In our center, every POTS patient is offered a visit to a psychologist. The psychologist can assess to which extent psychological issues may be involved in the etiology or maintenance of POTS. Clinical trials to identify the most effective psychological treatment enabling more specific referral and treatment are needed.

Pharmacotherapy may be required for patients who remain symptomatic after three months of optimal lifestyle interventions, or for patients whose severe symptoms hamper life style modifications even at earlier stages. Several drugs have shown a positive effect in POTS treatment, although one should keep in mind that the highest level of evidence is moderate and most options are based on non-interventional studies or expert opinions only (table 3). The most relevant options are shortly described below.

The best available evidence exists for low doses of short-acting beta blockers, in particular propranolol. It is mainly effective at lowering standing heart rate and improving complaints of palpitations. Interestingly, in a direct comparison, propranolol was inferior to exercise therapy. In this study, the combination of exercise and propranolol was not studied, contrasting with our recommendation to first optimize lifestyle before considering pharmacotherapy. High doses (≥ 80mg) of propranolol fail to show further improvement and may even worsen symptoms. Fludrocortisone, a mineralocorticoid, can be used when hypovolemia is suspected, to enhance sodium retention and to promote intravascular volume expansion. However, it can exacerbate headaches and vertigo, particularly in patients with migraine. Incidentally, desmopressin can be used to reach rapid volume expansion. Ivabradine, a selective sinus node inhibitor can slow heart rate without effecting blood pressure and seems to have a beneficial effect on fatigue. When symptoms are severe due to high sympathetic nervous system activity, central sympatholytic agents, clonidine and methyldopa, can be prescribed. In patients who are refractory to other commonly-used medications, the use pyridostigmine, a peripheral acetylcholinesterase inhibitor, can be considered. Stimulating agents such as modafinil or methylphenidate may be considered to improve concentration and reduce mental clouding, although its mechanism is unknown. One should keep in mind that modafinil may aggravate the orthostatic tachycardia since tachycardia is a well known side effect, although this was not shown in a small trial focused on safety in patients with POTS.

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Diagnosis to be excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td>History focused on possible causes of orthostatic tachycardia, salt and fluid intake, impact on daily activities and family history</td>
<td>Underlying cardiac disease including arrhythmia such as inappropriate sinus tachycardia syndrome or conduction abnormalities^6</td>
</tr>
<tr>
<td>Physical examination including stand test: BP and HR measurement supine and after 1, 3, 5 and 10 minutes of standing</td>
<td>Adrenal insufficiency (if suspicion, additional testing) Triggers inducing tachycardia (drugs, diet)</td>
</tr>
<tr>
<td>ECG</td>
<td>Hypothyroidism or hyperthyroidism</td>
</tr>
<tr>
<td>Blood test for other causes of orthostatic intolerance: Hb, TSH</td>
<td>Anemia</td>
</tr>
</tbody>
</table>

On indication:

- (Nor)metanephrine (plasma or urine)
- Tilt table test (most important indication: inability to stand)
- 24-hour Holter monitoring, additional cardiac screening

BP = blood pressure; HR = heart rate; ECG = electrocardiogram; Hb = hemoglobin; TSH = thyroid stimulating hormone

Table 2. Diagnostic approach

<table>
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<tr>
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<th>Diagnosis to be excluded</th>
</tr>
</thead>
<tbody>
<tr>
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BP = blood pressure; HR = heart rate; ECG = electrocardiogram; Hb = hemoglobin; TSH = thyroid stimulating hormone
Van der Zalm et al. POTS: a common, yet unfamiliar syndrome

Quality of life

POTS patients are limited in their physical activities and can become deconditioned over time.1,12,42 Unsurprisingly, quality of life in patients with POTS is low. Benrud-Larssen et al. reported that patients with POTS and patients with congestive heart failure had comparable physical and psychological composite scores.44 No correlation was found between quality of life and the maximal increase in heart rate.45 Despite the low quality of life, the prognosis of POTS is favorable, since 60% of the patients return with the given lifestyle and pharmacological options within five years to their level of functioning before onset; this should be emphasized to patients.4,50 However, resolution of symptoms as illustrated in the patients above is not always the case, and may lead to a more complex and chronic condition frustrating both patient and physician.

Table 3. Treatment options for POTS patients

<table>
<thead>
<tr>
<th>Treatment option</th>
<th>Recommendation</th>
<th>Remarks</th>
<th>Level of evidence*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lifestyle</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluid intake</td>
<td>At least 2-3 l, daily</td>
<td>When hypovolemia suspected (majority of patients)</td>
<td>Expert opinion1,3,9,16</td>
</tr>
<tr>
<td>Salt (NaCl) intake</td>
<td>Circa 10 grams daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical conditioning</td>
<td>Preferably horizontal activity, 20-30 minutes, 3 times a week</td>
<td></td>
<td>Moderate43-44</td>
</tr>
<tr>
<td>Compression stockings</td>
<td>Waist-high style stockings (pressure 30 to 40 mmHg)</td>
<td></td>
<td>Expert opinion13</td>
</tr>
<tr>
<td>Psychological interventions</td>
<td>Focused on coping mechanisms and somatic hypervigilance</td>
<td></td>
<td>Expert opinion3,8,45,46</td>
</tr>
<tr>
<td><strong>Pharmacological options</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td>20 mg daily</td>
<td>Only if blood pressure is sufficient High dose (≥ 80 mg) may worsen symptoms</td>
<td>Moderate44</td>
</tr>
<tr>
<td>Fludrocortisone</td>
<td>Start 50-62.5 µg/day to max 300 µg daily</td>
<td>When hypovolemia suspected. Caution in patients with migraine. Side effects include hypokalemia, severe headaches and vertigo</td>
<td>Expert opinion1,3,9,12,42</td>
</tr>
<tr>
<td>Desmopressin</td>
<td>0.2 mg</td>
<td>Side effects include hyponatremia. Only for occasional usage</td>
<td>Moderate45</td>
</tr>
<tr>
<td>Ivabradine</td>
<td>Start 2.5 mg once or twice daily (lower than in case of heart failure)</td>
<td>Potentially beneficial for fatigue, may result in visual abnormalities</td>
<td>Weak46</td>
</tr>
<tr>
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bid = twice a day; tid = three times a day
* Scoring of evidence is as follows: moderate = one randomized controlled trial; weak = only small non-interventional studies; expert opinion = no specific studies in POTS, in most cases based on experience in orthostatic hypotension

peripheral α1-adrenergic agonist midodrine may elicit vasoconstriction by reducing venous pooling, especially in neuropathic POTS.19 As most POTS patients are between 20 and 40 years of age, its major side effect (e.g., urinary retention due to prostatic hypertrophy) is not an issue.2,6
CONCLUSION

In conclusion, POTS is a heterogeneous clinical syndrome that overlaps with multiple syndromes such as chronic fatigue syndrome and Ehlers-Danlos syndrome. The diagnosis can be made in most cases by a thorough history, physical examination and a limited amount of additional testing to rule out other causes of orthostatic intolerance. Currently, there is not one standard treatment, but a treatment plan should entail lifestyle recommendations and psychological treatment. Pharmacological treatment is reserved for the patients who remain symptomatic despite these interventions. Especially in current times of self-diagnosing and ‘self-educated’ patients who are familiar with this syndrome, clinicians should not only be well informed and aware of POTS, but also familiar with its multifactorial background and treatment options in order to optimize therapy options for their patients.

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REFERENCES


REVIEW

Diagnosis and treatment of C3 glomerulopathy in a center of expertise

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ABSTRACT

C3 glomerulopathy is a rare renal disease that has been distinguished as a renal disease for about 10 years. It is caused by an excessive activation of the alternative complement pathway in the circulation, which leads to deposition of complement factor C3 in glomeruli. It is diagnosed based on clinical presentation, histological patterns in a kidney biopsy and tests of the complement pathways. It can closely resemble immune complex-mediated glomerulonephritis and postinfectious glomerulonephritis. Renal failure develops in up to half of all patients within 10 years after presentation. A curative treatment is not available. Treatment relies on renoprotective measures, occasional immunosuppressive medication and experimental novel complement inhibitors. Because the disease is rare, its care and cure are concentrated in centers of expertise. Here we provide an overview of the state-of-the-art diagnosis and treatment of C3 glomerulopathy in a center of expertise in the Netherlands.

KEYWORDS

C3 glomerulonephritis, C3 glomerulopathy, center of expertise, dense deposit disease, membranoproliferative glomerulonephritis

INTRODUCTION

C3 glomerulopathy is a rare renal disease that has been distinguished for about 10 years, when its pathophysiology was discovered to differ from other types of membrano-proliferative glomerulonephritis. C3 glomerulopathy appears to be caused by deposition of complement factor C3 without other complement factors or immunoglobulins in the glomeruli, as explained hereafter. Knowledge and comprehension of this disease are rapidly evolving. According to the Dutch National Plan on Rare Diseases, centers of expertise are allocated by the Ministry of Health in consultation with the European organisation for the care for rare diseases, Orphanet and the Dutch organisation for patients with rare diseases (Vereniging Samenwerkende Ouder-en Patiëntenorganisaties, VSOP). The national centers of expertise strive to collaborate within a European Reference Network. Because C3 glomerulopathy is a rare and new disease, clinical and scientific expertise are concentrated in such centers. Radboud University Medical Center (Radboudumc) and Leiden University Medical Center (LUMC) are centers of expertise on C3 glomerulopathy in the Netherlands. This review provides a succinct overview of the current diagnosis and treatment of C3 glomerulopathy at LUMC.

EPIDEMIOLOGY

The incidence of C3 glomerulopathy has been estimated at 1-2 per million per year. It is diagnosed in 1-2% of kidney biopsies. C3 glomerulopathy typically occurs in childhood or adolescence, but may also be diagnosed at older ages due to slow disease progression. It occurs equally in men and women, predominantly in Caucasian ethnicities and sometimes with a familial distribution. It commonly presents after an infection, which is thought to be a precipitating or eliciting risk factor, as in other glomerulonephritides. No specific types of
infections have been associated with C3 glomerulopathy, although respiratory tract infections seem most common. Other possible risk factors include vaccination, immunosuppressive, cytotoxic, and contraconceptive medication, pregnancy and childbirth.

PATHOPHYSIOLOGY

C3 glomerulopathy is caused by excessive activation of the alternative complement pathway. The complement pathways comprise circulating factors that sequentially activate each other in order to eliminate pathogens and damaged cells, and to guide and regulate immune cells and antibodies. Extensive reviews of the complement pathways are available elsewhere; a brief overview is given here and in figure 1. The alternative pathway is continuously active at a low level. Complement factor C3 is cleaved into C3a and C3b. C3a is an anaphylatoxin with proinflammatory and procoagulant effects. C3b binds factor Bb, after which, the complex C3bBb amplifies the pathway by cleaving additional C3 and creating more C3b and C3bBb. Because of this action, C3bBb is called C3 convertase. Large amounts of C3a and C3b can be formed, since C3 is abundant in plasma, accounting for approximately 2% of all proteins.

Because of its continuous spontaneous activity, regulatory factors suppress the activity of the alternative pathway in order to terminate its effects after the elimination of a pathogen or damaged cell, and to avoid harmful effects to other cells. C3 glomerulopathy may arise when a mutation renders such a factor deficient or dysfunctional; this has been shown in animal models and also observed in families with inherited C3 glomerulopathy. Most mutations affect circulating factor H. Mutations of thrombomodulin – known for its role in coagulation – can enhance the activity of the suppressing factor I. Mutations of C3 can make it resistant to a suppressing regulatory factor.

Other regulatory factors enhance the activity of the alternative pathway. C3 glomerulopathy may arise when a mutation renders factor B, factor H-related factor (CFHR) or properdin hyper-functional or increases the susceptibility of C3 to one of these enhancing regulatory factors.

Excessive activation of the alternative pathway may also be caused by autoantibodies. An autoantibody that binds and stabilizes C3 convertase is called C3 nephritic factor. Some C3 nephritic factors only bind C3 convertase in the presence of properdin. Other autoantibodies bind and eliminate suppressing regulatory factors like factor H, or bind and stabilize enhancing regulatory factors like factor B.

The classical pathway and the lectin pathway can activate the alternative pathway. These pathways are activated by antibodies, immune complexes, or components of pathogens or damaged cells. Their activation results in the formation of the C4bC2a complex, which cleaves C3 and creates more C3b and C3bBb. C4bC2a is therefore also called C3 convertase of the classical pathway. Autoantibodies that bind and stabilize this C3 convertase are called C4 nephritic factor. Confusingly, properdin-dependent C3 nephritic factor is sometimes also called C5 nephritic factor, as it is related to excessive activation of the terminal pathway. A mutation or autoantibody alone is insufficient to cause C3 glomerulopathy. They occur in other kidney diseases, as well as in apparently healthy persons, some in up to 8% of the general population. Multiple mutations, autoantibodies or additional genetic and environmental risk factors that activate complement factors – such as an infection – are thought to be required to elicit C3 glomerulopathy. Despite these insights into its pathophysiology, the predisposing and/or eliciting causes of C3 glomerulopathy remain unknown in many patients, more often so in adults than children.

CLINICAL PRESENTATION

The presentation of C3 glomerulopathy varies widely. It can present with signs of a nephritic syndrome, including proteinuria (90-95%), microscopic (64-88%) or macroscopic hematuria (16-38%), renal impairment (14-59%) and hypertension (21-46%). A nephritic syndrome is found in 27-55%.

Reports of the duration of symptoms until diagnosis differ between less than a year and multiple years. Children usually have a milder and slower course of disease than adults. For all patients suspected of C3 glomerulopathy – and likewise any glomerular disease – we evaluate the presence of these symptoms, general symptoms of autoimmune disease and the risk factors mentioned before (table 1).

In up to one-third of adult patients with C3 glomerulopathy, a monoclonal gammopathy is found, with increasing numbers at older ages. The gammopathy most commonly occurs without a lymphoproliferative malignancy, which would previously
Figure 1. Schematic overview of the function and dysfunction of the alternative pathway in C3 glomerulopathy. The alternative pathway (dark grey) is continuously active due to spontaneous cleavage of complement factor 3 (C3) into C3b, after which C3b binds factor B to form C3bBb. The classical pathway and lectin pathway (light grey) are activated when an antibody, immune complex, pathogen or damaged cell binds C1 or mannose-binding lectin (MBL), which leads to cleavage of C2 and C4, after which, they form C4bC2a. The alternative pathway is amplified by two different C3 convertases generated by one of the three pathways (C3bBb for the alternative and C4bC2a for the classical and lectin pathways). By cleaving more C3 and formation of C5 convertase (C3bBbC3b or C4bC2aC3b), all pathways lead to activation of the terminal pathway, which ends in the formation of the complex C5b-9 or the membrane attack complex. The processes are enhanced by the regulatory factors in green and suppressed by those in red. The nephritic factors (NeF) are autoantibodies that bind and stabilize the convertases, thereby preventing their cleavage. Regulatory factors suppress (red) or enhance (green) the processes. Factor H (FH) inhibits the binding of C3b with factor B, enhances the dissociation of C3 convertase and enhances the activity of circulating factor I. Factor I (FI) cleaves C3b into inactivated C3b (iC3b). Membrane cofactor protein (MCP, also called CD46), decay accelerating factor (DAF, also called CD55) and complement receptor 1 (CR1, also called CD35) enhance the dissociation of C3 convertase and/or the activity of factor I. Properdin (P) enhances the formation of C3 convertase and stabilizes it, thereby preventing the action of factor H, decay accelerating factor and complement receptor 1. The family of five factor H-related factors (CFHR) inhibits the action of factor H. Clusterin (Cltn), protectin (Prtn) and vitronectin (Vtrn) inhibit the formation of the membrane attack complex, but their dysfunction has thus far not been related to C3 glomerulopathy.7,17,20-24,46
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AP50 = activity of the alternative complement pathway; C1q = one of the constituents of C1; C3c and C3d = breakdown products of C3b; C4d = a breakdown product of C4; CFHR1-5 = complement factor H-related factors 1 through 5; CH50 = activity of the classical complement pathway; MLPA = multiplex ligation-dependent probe amplification
have been considered a monoclonal gammopathy of undetermined significance, but is now, in the presence of renal disease, called a monoclonal gammopathy of renal significance. Among patients aged 50 years and older, the gammopathy is a monoclonal gammopathy of renal significance in 44–83%, a multiple myeloma in 44% and another malignancy in 11-17%, all without cast nephropathy or glomerular deposition of immunoglobulins or light chains.\textsuperscript{3,6-7,37,40} The paraprotein is thought to act as an autoantibody that inhibits regulatory factors, stabilizes C3 convertase like C3 nephritic factor, or cleaves C3 and consequently activates the alternative pathway.\textsuperscript{3,7-9,34,35} All patients should be tested for the presence of monoclonal gammopathy using protein electrophoresis.\textsuperscript{79}

Ocular drusen and acquired partial lipodystrophy are associated with C3 glomerulopathy. Ocular drusen are deposits of complement factors between the retinal epithelium and the underlying Bruch’s membrane. Drusen resemble the deposits of complement factors in the glomeruli, discussed hereafter, and are a result of the structural and functional similarities between the Bruch’s membrane and the glomerular basement membrane. Drusen are also found in age-related macular degeneration, but occur in younger C3 glomerulopathy patients. They can lead to visual impairment.\textsuperscript{5,7-9,35-39} We refer patients to an ophthalmologist to be screened for drusen by fluorescein angiography and optical coherence tomography. Even in the absence of symptoms, screening for drusen may be helpful for timely prevention or treatment and for the diagnosis of C3 glomerulopathy. Acquired partial lipodystrophy involves the loss of subcutaneous fat from the face, neck, arms and trunk. Fat tissue is destructed by complement factors, perhaps because adipocytes themselves produce C3, factor B and C3 convertase.\textsuperscript{5,6,27,40} We examine patients for lipodystrophy.

**HISTOLOGICAL PATTERNS**

The excessive activation of the alternative complement pathway that characterizes C3 glomerulopathy results in deposition of complement factor C3 in glomeruli. Although the relation between histological patterns and clinical presentation remains unclear,\textsuperscript{67} a kidney biopsy is required to evaluate the presence, localization, and composition of the deposits and to confirm the diagnosis.\textsuperscript{47}

Furthermore, a kidney biopsy is the only method for distinguishing the two types of C3 glomerulopathy: dense deposit disease and C3 glomerulonephritis. Their differences in pathophysiology remain unclear,\textsuperscript{7,46} since neither their genetic cause\textsuperscript{6,9,20,46} nor clinical presentations differ, except that dense deposit disease is uncommonly seen in the presence of a monoclonal gammopathy and confers a lower risk of renal impairment.\textsuperscript{3,6-7,10,12,14}

Under light microscopy, C3 glomerulopathy presents as membranoproliferative glomerulonephritis in 44-76% of patients, mesangial proliferative glomerulonephritis in 21-28%, diffuse endocapillary proliferative glomerulonephritis in 8-19% and crescentic glomerulonephritis in 9%. Dense deposit disease presents more often with acute crescentic lesions, while C3 glomerulonephritis presents more often with chronic fibrotic and sclerotic lesions.\textsuperscript{3-6,10,12,27,28} Although, confusingly, the opposite has also been reported.\textsuperscript{11} Children present less commonly with glomerular and interstitial fibrosis than adults.\textsuperscript{5,93}

Immunohistology is used to identify the constituents of the glomerular deposits. Deposits of C3 and its breakdown products define C3 glomerulopathy,\textsuperscript{79} while deposits of C1 and C4 are scarce or absent.\textsuperscript{44} We have not routinely evaluated the presence of other complement factors. Deposits of C4 may be associated with monoclonal gammopathy.\textsuperscript{91} Deposits of C5b-9 are thought to reflect activation of the terminal pathway, but can also be found in apparently healthy kidneys and after kidney transplantation, particularly in vascular and fibrotic lesions, suggesting a role in tissue damage or tissue repair.\textsuperscript{19} Deposits of immunoglobulins occur in variable amounts and with uncertain relevance.\textsuperscript{8,9} Deposits of immunoglobulins are most common of the IgM type\textsuperscript{5,52} and are located subendothelially or subepithelially.\textsuperscript{4}

In addition to immunoglobulins, we evaluate the presence of light chains to unveil possible monoclonal gammopathy as an underlying cause of C3 glomerulopathy.\textsuperscript{77}

The presence of immunoglobulins or light chains may remain masked in routinely-used freshly frozen samples, and revealed only in formalin-fixed paraffin-embedded samples to which a protease has been added.\textsuperscript{6-44} The latter technique should therefore be considered, especially when a monoclonal gammopathy is not detected in the freshly frozen sample but suspected, for example, due to deposits of C4.\textsuperscript{92}

Studies of single glomeruli using mass spectrometry have confirmed that the deposits in C3 glomerulopathy consist of C3 and its breakdown products, together with C5b-9 and uncommonly C4, but not of immunoglobulins.\textsuperscript{30-34,44-45} By agreement, C3 glomerulopathy has been defined as a glomerulonephritis with dominant staining for C3 that is at least two orders of magnitude more intense than other complement factors, immunoglobulins or immune complexes.\textsuperscript{19} More strict definitions, excluding patients with any deposits of immunoglobulins, miss many probable cases of C3 glomerulopathy, although even the current definition may miss such cases.\textsuperscript{8,19}

Electron microscopy is used to localize the glomerular deposits.\textsuperscript{7} In dense deposit disease, by definition, the deposits are electron-dense and located within the glomerular basement membrane. C3 glomerulonephritis is characterized by less dense and less concrete granular deposits in the glomerular basement membrane.\textsuperscript{92,30-34,49}
and deposits in the mesangium, the subendothelial or subepithelial space. These deposits are found less often in dense deposit disease in addition to the electron-dense deposits in the glomerular basement membrane. Deposits are uncommonly found in Bowman’s capsule and the tubular basement membrane.

### TESTS OF THE COMPLEMENT PATHWAYS

Several tests of the complement pathways should be performed in all patients suspected of C3 glomerulopathy. Consistent with activation of the alternative pathway and glomerular deposition of C3, the serum level of C3 is reduced in the majority (41-76%), and the serum level of C4 is reduced in only a minority (1-23%) of patients. The level of C3 is more often reduced in children (83-100%) than adults (41-57%). Subsequent activation of the terminal pathway is reflected by a low level of C5 and an elevated level of circulating C5b-9. Unlike C3 and C4 levels, we have not measured the levels of C5 and C5b-9 routinely. The measurement of circulating C5b-9 is difficult, as it requires appropriate sampling, handling and storage of plasma to prevent iatrogenic activation of the complement pathways.

Helping to distinguish between both types, the level of C3 appears more often reduced in dense deposit disease and in patients with C3 nephritic factor. The level of C5b-9 appears higher in patients with C3 glomerulonephritis and in patients with a properdin-dependent C3 nephritic factor. These results suggest that the alternative pathway is activated more in the former category of patients and that the terminal pathway is activated more in the latter category of patients.

We measure the activity of the complement pathways as the hemolytic activity of a patient’s serum directed against animal erythrocytes. The so-called CH50 represents the activity of the classical pathway, while the AH50 or AP50 represents the activity of the alternative pathway.

We measure C3 nephritic factor and autoantibodies against factor H as potential causes of C3 glomerulopathy. C3 nephritic factor is present in 44-78% of patients, and more often in dense deposit disease (78-86%) than C3 glomerulonephritis (38-59%). and more often in children (91-100%) than adults (31-46%). Other types of nephritic factor are less common. Different types of nephritic factor can also be present simultaneously. Tests of C3 nephritic factor have not been standardized and vary between laboratories. Some laboratories run different tests in parallel. We make use of the tests at Sanquin or Radboudumc in the Netherlands or the University of Iowa, United States and repeat a test elsewhere if its result is uncertain. The tests are currently evaluated to enhance their reliability, to understand their comparability and to distinguish different types of nephritic factors. We incidentally measure other autoantibodies, like C4 nephritic factor or antibodies against factor B, if no other cause of C3 glomerulopathy has been found and if the presence of autoantibodies is suspected, for example, based on the presence of antinuclear antibodies.

We do not rely on other tests of the complement pathways, since these measurements can be performed in only a few laboratories and have not been validated. As part of the national COMBAT Consortium (COMplement: Basis mechanisms, Assay development and novel Therapy), we currently evaluate and implement novel tests.

### GENETIC TESTS

All patients require referral to a clinical geneticist to test for mutations, copy number variation, hybrid genes and other genetic rearrangements in the genes of complement factors, most specifically C3, factor B, factor H, factor I and CFHR. The processing time and the reliability of these tests are improving. Several additional alleles that confer an elevated risk of C3 glomerulopathy are only tested for research purposes.

### DIFFERENTIAL DIAGNOSIS

The aforementioned tests help to distinguish C3 glomerulopathy from other types of glomerulonephritides that may closely resemble C3 glomerulopathy and are also caused by excessive activation of complement factors, such as immune complex-mediated glomerulonephritis and post-infectious glomerulonephritis. Still, a distinction is often very difficult. Autoantibodies and genetic mutations do not consistently differ between these three types of glomerulonephritides. The clinical presentations are similar, except for a nephrotic syndrome occurring more often in immune complex-mediated glomerulonephritis than C3 glomerulopathy. In a kidney biopsy, deposits of C4 and its breakdown products, resulting from activation of the classical pathway, are thought to distinguish post-infectious glomerulonephritis and immune complex-mediated glomerulonephritis from C3 glomerulopathy, but not all studies have confirmed this distinction. In contrast with C3 glomerulopathy, the deposits in immune complex-mediated glomerulonephritis consist less commonly of C3 and C5b-9, more commonly of C1 and C4 and always of immunoglobulins. Subepithelial hump-like deposits as observed with electron microscopy have been thought to characterize post-infectious glomerulonephritis, but have also been reported in C3 glomerulopathy, both with and...
without a preceding infection. The serum levels of C3, C4, C5b-9 and C3 nephritic factor are similar. Post-infectious glomerulonephritis can sometimes only be discerned by its typical spontaneous resolution in six to twelve weeks. These three glomerulonephritides can even be found consecutively during the course of the disease, before and after kidney transplantation or in different patients within the same family. Whereas C3 glomerulopathy arises through excessive activation of the alternative pathway due to dysfunction of circulating complement factors, dysfunction of complement factors at the surface of cells can also lead to excessive activation of the alternative pathway, but this manifests as different diseases, such as atypical hemolytic uremic syndrome. Dysfunction of factors that can circulate and bind the membrane of a pathogen or damaged cell — including C3b, C3 convertase, and factor H — may give rise to either disease. Since the glomerular basement membrane lacks membrane-bound regulatory factors and easily captures circulating complement factors, it is dependent on circulating regulatory factors and affected in C3 glomerulopathy.

TREATMENT

No treatment has proven effective and beneficial for C3 glomerulopathy. Recommendations have only been deduced from case series and observational studies and are mostly based on expert opinion. As a consequence, its treatment has not been standardized and is concentrated in centers of expertise. All patients diagnosed with C3 glomerulopathy should be treated with renoprotective measures, including lifestyle advice, an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker to control hypertension and proteinuria, and lipid-lowering treatment. Such medication alone has not been shown to protect against progression to end-stage renal disease, but may improve the protective effect of immunosuppressive medication. When a monoclonal gammopathy is suspected to be an underlying cause of C3 glomerulopathy, the patient is referred to a hematologist. Its treatment is thought to be effective in patients with C3 glomerulopathy. In a retrospective study of 50 patients with C3 glomerulopathy and various types of monoclonal gammopathy, renal function and proteinuria improved more often with chemotherapy (74%) than with renoprotective or immunosuppressive medication (5%), and more often if the gammopathy was reduced (83%) than if it was not reduced (28%). The hazard of end-stage renal disease was 83% lower if the gammopathy was reduced. In a similar study of 33 patients, improvement of renal function and proteinuria was similar with (38%) and without chemotherapy (41%), and these improvements were seen more often if the gammopathy was reduced (40%) than if it was not reduced (0%). Chemotherapy is preferentially used to treat gammopathy due to lymphoproliferative malignancies, but the association between a reduction in gammopathy and an improvement of renal function suggests that chemotherapy may also be considered for the treatment of monoclonal gammopathy of renal significance.

If moderate inflammation is present in the kidney biopsy and proteinuria persists despite supportive treatment, or if renal function decreases, then prednisolone and/or mycophenolate mofetil are recommended. Neither immunosuppressive medication in general nor corticosteroids in particular have conferred consistent beneficial effects across various studies. According to two observational studies, mycophenolate mofetil — alone or in combination with prednisolone — offers better protection against renal impairment compared to prednisolone, cyclophosphamide, tacrolimus, cyclosporine or rituximab although this was not confirmed in a third study. If, despite treatment with prednisolone and mycophenolate mofetil, severe inflammation is present in the kidney biopsy and proteinuria persists, or renal function decreases, then methylprednisolone, cyclophosphamide, tacrolimus or rituximab can be considered, although a beneficial effect has not been confirmed. Despite this uncertainty, we prefer rituximab if autoantibodies are present.

Exceptional off-label use of eculizumab, a monoclonal antibody that inactivates C5, has been suggested for patients with C3 glomerulopathy. Its effects have not been studied in randomized trials. Case reports have described that it improves renal function and proteinuria. A retrospective study of 26 patients treated with eculizumab reported improvement of renal function and proteinuria in 46% and reduction of histological lesions in 82%. These effects were more often observed in those with a rapidly progressive course of disease and extra-capillary proliferation, without differences between children and adults. In the only prospective study performed in six patients, eculizumab improved renal function in two patients, partially resolved a nephrotic syndrome in a third; it also reduced histological lesions in the two patients with improved renal function and one other patient. Elevated levels of circulating C5b-9 were reduced, but deposits of C5b-9 in the kidney biopsies remained. Since eculizumab inhibits the terminal pathway, it is expected to benefit particularly those patients with activation of the terminal pathway, reflected by a high amount of C5b-9 in the circulation and kidney biopsy, which is more common in those with C3 glomerulonephritis. Various other complement inhibitors are currently being developed, including
inhibitors of C3, inhibitors of C5a and soluble inhibitory regulatory factors. Treatment with immunosuppressive medication or eculizumab confers a risk of infections, for which antibiotic prophylaxis, vaccination and cautious administration during active infection are indicated. We vaccinate against Streptococcus pneumoniae, Neisseria meningitidis, and Haemophilus influenzae. Eculizumab has no other known side effects. If renal function is acutely impaired, especially if crescentic lesions are present in the kidney biopsy, plasmapheresis can be considered in addition to immunosuppressive medication. Plasmapheresis is expected to be beneficial in cases of dysfunction or deficiency of complement factors or regulatory factors, although this has only been demonstrated in some case reports.

Kidney transplantation is performed in more than half of patients who have reached end-stage renal disease. Unfortunately, C3 glomerulopathy often recurs after kidney transplantation, histologically in 67-90% and clinically in 50-60% of patients. It recurs more often in dense deposit disease than C3 glomerulonephritis and in patients with a mutation of a complement factor. The transplant is lost due to recurrence in about 50% of patients, which is a large proportion as compared with other glomerulonephritides. The median time of survival of the transplants is around five years; less than a third has survived after 10 years.

**PROGNOSIS**

With the aforementioned treatments, clinical remission of C3 glomerulopathy is reached in 55-62%, with complete remission in 22-32% after two to four years, or in 35% after six years, with complete remission in 15% of patients. Chronic treatment with immunosuppressive medication is necessary in half of the patients to sustain remission. Remission is more often achieved in C3 glomerulonephritis than dense deposit disease. Spontaneous remission occurs in rare instances. C3 glomerulopathy leads to end-stage renal disease in 11-52% of patients in, on average, six to ten years. Risk factors of end-stage disease are older age, renal impairment, heavy proteinuria at presentation, little reduced serum levels of C3 and C5b-9, glomerular sclerosis or crescents, interstitial fibrosis or tubular atrophy, glomerular deposition of C3 without immunoglobulins, monoclonal gammopathy, and the absence of C3 nephritic factor or mutations of complement factors. Both a nephrotic and nephritic syndrome have been associated with a worse prognosis. Unfortunately, in clinical practice, neither the presentation nor the results of the aforementioned tests can predict the course of the disease or the effects of treatment.

**ACKNOWLEDGMENTS**

The description of the histological patterns of C3 glomerulopathy was reviewed by Dr. Ingeborg M. Bajema, Department of Pathology, Leiden University Medical Center, Leiden, the Netherlands. Research on C3 glomerulopathy at LUMC is conducted as part of the COMplement: Basic mechanisms, Assay development and novel Therapy Consortium (COMBAT Consortium), funded by the Dutch Kidney Foundation. This review was written without funding.

**DISCLOSURES**

The authors have no funding or conflicts of interests to disclose.

**REFERENCES**


Introduction of routine hepatitis B screening for all patients receiving cancer treatment


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ABSTRACT

Background: Patients with a chronic hepatitis B virus (HBV) infection or patients who have recovered from an HBV infection are at risk for HBV reactivation (HBVr), especially if they need treatment with chemotherapy. International guidelines recommend routine HBV screening for all patients starting with chemotherapy. This study evaluates the implementation of a routine HBV screening protocol.

Methods: A retrospective study was performed between January 2015 and October 2016 at the Medical Centre Slotervaart Amsterdam. All patients with a solid or hematological malignancy starting intravenous chemotherapy were included. In September 2015, a protocol for routine HBV screening was introduced. HBV screening results were evaluated before and after implementation of the screening protocol.

Results: In total, 184 patients were included, of which 129 patients were actually screened; 37 of the 70 (53%) patients were screened in the group before implementation of the protocol and 92 of the 114 (81%) after implementation. Before routine HBV screening, 8/37 (21.6%) patients tested anti-HBc positive; after introduction of routine screening, 13/92 (14.1%) patients tested anti-HBc positive. After implementation of the screening protocol, no HBVr occurred.

Conclusion: Implementation of routine HBV screening in patients starting chemotherapy increases identification of the number of patients identified as at risk for HBVr and contributes to prevention of HBVr. A high prevalence of anti-HBc positive patients was found during routine HBV screening, indicating the importance of screening. Awareness and implementation of routine HBV screening, together with knowledge of existing guidelines is necessary to increase the HBV screening rate in patients treated with chemotherapy.

KEY WORDS

Hepatitis B reactivation, immunosuppressive therapy, screening

INTRODUCTION

Infection with hepatitis B virus (HBV) is a global public health problem that leads to significant morbidity and mortality. According to the World Health Organization (WHO), an estimated 240 million people are chronically infected with hepatitis B worldwide. The regional endemic variation of hepatitis B infected patients is large, with currently changing prevalence and incidence in low endemic countries as a result of the higher hepatitis B prevalence in migrants and refugees. According to the Pienter studies, prevalence in the Netherlands in 2007 was 0.2% for a chronic HBV infection (positive hepatitis B surface antigen, HBsAg), and 3.5% for patients ever exposed to HBV (antibodies to hepatitis B core antigen, anti-HBc). A significantly higher prevalence was observed within the population of non-Western immigrants and high-risk groups. Both patients with a chronic HBV infection and patients exposed to HBV (with or without antibodies to HBsAg (anti-HBs)) are at risk for reactivation. Reactivation is generally defined as a detectable HBV-DNA level in patients with a previously undetectable HBV-DNA level, a significant increase of HBV-DNA (> 10 fold or > 2,000 IU/ml) and/or the reappearance of HBsAg in a previously negative individual. Known risk factors for reactivation are immuno- or chemotherapy, organ transplantation and other infectious diseases such as HIV and hepatitis C. A considerable number of patients are unaware of their HBV status and the risk factors for HBV infection. In particular, patients treated with B-cell depleting agents such as rituximab or combined immunosuppressive...
therapy containing steroids are at risk for reactivation of HBV (HBVr).\textsuperscript{9-11} Reactivation can cause a fulminant infection that can lead to severe liver failure and even death, with a mortality rate of up to 25%.\textsuperscript{9} Furthermore, chemotherapy treatment may be interrupted or delayed in cases of HBVr.

Selective screening for at risk patients is ineffective and high-risk patients are not always correctly assessed or recognized.\textsuperscript{9} Therefore, current international guidelines recommend a routine HBV screening procedure for every patient planned to receive cancer treatment. \textsuperscript{4,10-14} Recently, a Dutch HBV guideline based on the guidelines of the European Association of the Study of the Liver (EASL) was published and states that all patients must be screened for HBV before the start of chemotherapy.\textsuperscript{4} Despite the realization that routine screening for both solid and hematological malignancies is needed, the actual screening rate by oncologists remains low, 13-19%.\textsuperscript{15,16} Oncologists who experienced HBVr in a patient were more likely to screen all patients compared to oncologists who did not.\textsuperscript{16}

In our hospital, a routine HBV screening protocol was introduced for every patient initiated for any type of chemotherapy in September 2015, after two cases of HBVr occurred. The first case was a North-African woman treated with a rituximab-containing regimen; this patient died as a consequence of severe liver failure. The other patient experienced transient liver failure after treatment with doxorubicin, cyclophosphamide and paclitaxel.\textsuperscript{57} Before routine HBV screening, only high-risk patients were screened, mainly based on ethnicity or type of immunosuppressive therapy.

In this retrospective study we report the incidence of a positive test result at screening for hepatitis B, defined as HBsAg positive and/or anti-HBc positive, in patients who started chemotherapy in our hospital. Furthermore, we will evaluate the introduction of routine HBV screening in all patients.

MATERIALS AND METHODS

Study population

A retrospective study was performed to investigate the incidence of a positive test result at screening for HBV in a patient population receiving chemotherapy. This study was carried out in the Medical Centre Slotervaart Amsterdam, a teaching hospital, in the internal medicine department. All patients who started with intravenous chemotherapy between January 2015 and October 2016 were included. This study was approved by the accredited Medical Ethics Committee of the hospital.

Hepatitis B screening

Before September 2015, patients were screened for HBV if they were considered high-risk patients by the treating physician. From that date on, a protocol for routine screening was introduced. A meeting was organized to inform all involved parties about the protocol and the protocol was published on the hospital’s document management system to be easily accessible for all healthcare providers within the hospital. We defined two different groups of patients: patients before the introduction of the protocol for HBV screening and patients after introduction of the protocol for HBV screening.

The standard HBV screening consists of HBsAg, anti-HBc and anti-HBs. If either the HBsAg and/or anti-HBc were positive, an HBV-DNA test was ordered. We used the Liaison XL test (DiaSorin, Sallugia, Italy) for hepatitis B serology, and the Abbott m2000 sp/rt system (Abbott Laboratories) for viral load (HBV DNA). The cut-off values were: HBsAg in IU/ml: < 0.05 was negative and > 0.05 was positive; anti-HBs in mIU/ml: < 9 was negative, ≥ 9 and ≤ 10 was equivalent and > 10 was positive. For anti-HBc, a qualitative test was performed with a positive or negative test result. HBV-DNA ≤ 10 IU/ml was considered negative. If a patient tested positive for anti-HBc, a standard follow-up with liver serum transaminases and three, monthly HBV-DNA tests were performed. Antiviral prophylactic therapy with tenofovir was started in patients with a positive HBsAg test or a positive HBV-DNA test, and in patients who were anti-HBc positive and started high-risk therapy.

Data collection

Patients who received their first chemotherapy treatment between January 2015 and October 2016 were identified through a database of the oncology department. The data were collected through the electronically registered medical records. Test results of HBV screening were recorded for every patient as well as patient characteristics including age, sex, nationality and type of cancer.

Two groups were defined based on the endemic appearance of hepatitis B in the patients’ country of birth: low endemic regions (< 2%) and high endemic regions (> 2%). Countries with a prevalence of chronic HBV infection (< 2%) were considered as low endemic (Western Europe and North America). Countries with a prevalence of chronic HBV infection of > 2% were considered as high endemic (Eastern Europe, Asia, Africa, South America, Middle East and the Caribbean).

Data analysis

Descriptive statistics were used to give an overview of the patient characteristics in this study. Categorical data were reported as numbers and percentages. Continuous data such as age were reported as median and interquartile range (IQR). To compare the isolated anti-HBc positive patients with the anti-HBc and anti-HBs positive patients.
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we used the independent t-test for the continuous normal distributed variables and the Chi-Square test or Fisher’s exact test for the categorical variables, depending on the number of cases. All analyses were performed with IBM SPSS statistics (version 24).

**RESULTS**

**Patient characteristics**
In total, we included 184 patients with a solid or hematological malignancy for which they received their first treatment with intravenous chemotherapy at the Medical Centre Slotervaart between January 2015 and October 2016. Routine HBV screening for all patients was introduced in September 2015. The patients were divided in two groups: patients who started treatment before introduction of the screening protocol (group ‘before’) and the patients who started treatment after introduction of the screening protocol (group ‘after’) (*table 1*).

**Screening procedure**
Overall, 129 patients were screened for HBV according to the local screening procedure, 70 in the group ‘before’ and 114 in the group ‘after’. In the group ‘before’, 52.9% (37/70) of the patients were screened, and in the group ‘after’, 80.7% (92/114) of the patients were screened. The median age in both groups was approximately 60 years. In both groups, 64% of the patients were female. The most common malignancies were breast cancer, lung cancer, hematological cancer and colorectal cancer. Three-quarters of the patients were born in a low endemic country and 22% of the patients were born in a high endemic region.

Before introduction of the protocol for routine screening, the overall percentage of patients screened for HBV was 52.9%. Almost all hematological patients were screened (91%), while the HBV screening rate of patients with solid tumors ranged from 22-58% (*table 1*). After introduction of the protocol in September 2015, the percentage of patients that were actually screened increased to 80.7%. The screening rate in patients with solid tumors increased from 22-58% to 42-98%. The screening rate in patients born in non-endemic areas increased from 48% in the group ‘before’ to 79% in the group ‘after’. Patients with a lung tumor were screened in 42% of the group ‘after’ cases; this was the lowest screening rate reported in the group after introduction of the protocol. The hematological patient group was the only group with a decrease in screening rate, from 91% to 80%.

### Table 1. Basic patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Before protocol (Jan 2015 - Sep 2015)</th>
<th>After protocol (Sep 2015 - Oct 2016)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Screened</td>
<td>Not screened</td>
</tr>
<tr>
<td>Total patients: n (%)</td>
<td>37 (52.9)</td>
<td>33 (47.1)</td>
</tr>
<tr>
<td>Age, median (IQR)</td>
<td>60 (49-67.5)</td>
<td>67 (59.5-74)</td>
</tr>
<tr>
<td>Male: n (%)</td>
<td>9 (37.5)</td>
<td>15 (62.5)</td>
</tr>
<tr>
<td>Female: n (%)</td>
<td>28 (61)</td>
<td>18 (39)</td>
</tr>
<tr>
<td>Primary tumor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung: n (%)</td>
<td>3 (25)</td>
<td>9 (75)</td>
</tr>
<tr>
<td>Hematological: n (%)</td>
<td>10 (91)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>Breast: n (%)</td>
<td>18 (58)</td>
<td>13 (42)</td>
</tr>
<tr>
<td>Colon: n (%)</td>
<td>2 (22)</td>
<td>7 (78)</td>
</tr>
<tr>
<td>Other/undefined: n (%)</td>
<td>4 (57)</td>
<td>3 (43)</td>
</tr>
<tr>
<td>Endemic⁴</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 2%: n (%)</td>
<td>25 (48)</td>
<td>27 (52)</td>
</tr>
<tr>
<td>&gt; 2%: n (%)</td>
<td>10 (77)</td>
<td>3 (23)</td>
</tr>
<tr>
<td>Unknown: n (%)</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

n = number of patients; IQR = inter quartile range

⁴Endemic regions: < 2% = low endemic area (prevalence chronic HBV infection of < 2%); > 2% = high endemic area (prevalence of chronic HBV infection of > 2%)
None of the 129 patients screened for HBV were HBsAg positive. Overall, 21 (16.3%) patients were anti-HBc positive and were therefore considered to be at risk for HBVr (Table 2). In the group ‘before’, 8/37 (21.6%) of the screened patients tested positive for anti-HBc, of which five patients were both anti-HBc and anti-HBs positive and three patients were only anti-HBc positive (isolated anti-HBc). All of these patients tested negative for HBV DNA (HBV-DNA < 10 IU/ml). One of the three patients with an isolated anti-HBc started prophylactic antiviral therapy because of treatment with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP).

In the group ‘after’, 13/92 (14.1%) of the screened patients tested positive for anti-HBc of which eight patients were both anti-HBc and anti-HBs positive and five patients were isolated anti-HBc positive. One of these five patients had HBV DNA levels > 10 IU/ml and started with prophylactic tenofovir before the start of chemotherapy. In this group, nine patients (7%) were isolated anti-HBs positive, most likely indicating a post-vaccination status.

### Table 2. Positive screening results

<table>
<thead>
<tr>
<th></th>
<th>Before protocol</th>
<th>After protocol</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screened patients: n (%)</td>
<td>37 (52.9)</td>
<td>92 (80.7)</td>
<td>129 (70.1)</td>
</tr>
<tr>
<td>Serology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated anti-HBc (n)</td>
<td>3</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Anti-HBc + anti-HBs (n)</td>
<td>5</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>HBV DNA &gt; 10 IU/ml (n)</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total positive anti-HBc: n (%)</td>
<td>8 (21.6)</td>
<td>13 (14.1)</td>
<td>21 (16.3)</td>
</tr>
<tr>
<td>Isolated anti-HBs (n)</td>
<td>0</td>
<td>9</td>
<td>9</td>
</tr>
</tbody>
</table>

n = number of patients; anti-HBc = antibodies to the hepatitis B core antigen; anti-HBs = antibodies to the hepatitis B surface antigen; HBV DNA = hepatitis B virus DNA

### Serology results

None of the 129 patients screened for HBV were HBsAg positive. Overall, 21 (16.3%) patients were anti-HBc positive and were therefore considered to be at risk for HBVr (Table 2). In the group ‘before’, 8/37 (21.6%) of the screened patients tested positive for anti-HBc, of which five patients were both anti-HBc and anti-HBs positive and three patients were only anti-HBc positive (isolated anti-HBc). All of these patients tested negative for HBV DNA (HBV-DNA < 10 IU/ml). One of the three patients with an isolated anti-HBc started prophylactic antiviral therapy because of treatment with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP).

In the group ‘after’, 13/92 (14.1%) of the screened patients tested positive for anti-HBc of which eight patients were both anti-HBc and anti-HBs positive and five patients were isolated anti-HBc positive. One of these five patients had HBV DNA levels > 10 IU/ml and started with prophylactic tenofovir before the start of chemotherapy. In this group, nine patients (7%) were isolated anti-HBs positive, most likely indicating a post-vaccination status.

### Anti-HBc positive

Because of the known risk of reactivation in patients with a positive anti-HBc, we will highlight this specific subgroup of 21 patients. The median age of these patients was 60 years old. Seven of these patients were born in a non-endemic region. Eight patients tested isolated anti-HBc positive, and five of these patients were born in a non-endemic area and three in an endemic area.

The age of patients with an isolated anti-HBc was significantly higher compared to patients with both a positive anti-HBc and anti-HBs, respectively 73 years and 53 years (p-value < 0.01). No significant difference was found for endemic background between patients with an isolated anti-HBc and patients with both a positive anti-HBc and anti-HBs.

Within the total anti-HBc positive group of patients, one patient had a history of a recovered HBV infection and one patient was known to have a concomitant HIV infection.

### Reactivation and one-year follow-up

Within this study cohort, one patient suffered from an HBVr in the group before introduction of the routine HBV screening protocol. This patient was not screened before the start of the chemotherapy treatment for breast cancer with 4x doxorubicin/cyclophosphamide and 12x paclitaxel. The reactivation occurred one month after the last chemotherapy. From a stored blood sample, it was determined that the anti-HBc and anti-HBs (112 mIU/ml) were positive before start of the chemotherapy. During reactivation, the HBV DNA viral load reached almost 1,000,000 IU/ml and the anti-HBs test was negative. This patient was immediately started on tenofovir 245mg once daily for a period of 12 months and she fully recovered with a re-seroconversion to anti-HBs.

A one-year follow-up was performed in the 21 patients with a positive anti-HBc test. In this group, two patients started tenofovir prophylaxis. The first patient was prone for reactivation because of a positive anti-HBc, a negative anti-HBs and a detectable HBV-DNA viral load between 10 IU/ml and 15 IU/ml. This patient was prescribed tenofovir 245 mg once daily at the start of chemotherapy until 12 months after the last chemotherapy (R-miniCHOP). The other patient who received tenofovir was initiated for the high-risk R-CHOP chemotherapy and tested isolated anti-HBc positive with an HBV-DNA viral load < 10 IU/ml. The HBV-DNA viral load was undetectable during follow-up after start of chemotherapy in all other patients.
DISCUSSION

In the present study, we evaluated the introduction of a protocol for routine HBV screening in patients before start of medical cancer treatment in our hospital. Introduction of the screening protocol did not guarantee that all patients were screened. After introduction of the protocol, the screening rate increased from approximately 50% to 80%, but did not reach the desired 100% screening rate. This suboptimal screening rate can be partly explained by the low screening rate of patients with lung tumors (42%) compared to other solid tumors or hematological malignancies (80-98%). Dutch treatment guidelines for lung tumors do not mention hepatitis B screening before start of therapy, although HBVr during lung cancer chemotherapy has been described. In recent years, national and international guidelines have started to recommend routine HBV screening before start of chemotherapy. However, these guidelines were written by international liver associations and have been published in their official journals. We believe that attention for HBV screening in oncology journals and/or implementation in oncology guidelines is needed to increase awareness amongst oncologists, as Van Roon et al. did in The Dutch Journal for Oncology. Another observation was the decreased screening rate in patients with a hematological malignancy. Although the screening protocol was introduced, two patients received high-risk chemotherapy without HBV screening. In order to achieve a 100% screening rate, we organized a meeting to notify the involved doctors and oncology nurses about our findings and to discuss possible improvements for the HBV screening protocol. We have strongly advised to include HBV screening as a mandatory field on the checklist for every oncology patient. In addition, an automated warning system to check HBV status in the electronic patient record before chemotherapy prescription will help improve results.

A remarkable result of this study was the high prevalence (14%) of anti-HBc positive patients within the screened patients after introduction of the protocol. This is much higher compared to the incidence in the general Dutch population (3.5% in 2007). The fact that our hospital is located in a multi-ethnic area with many first- and second-generation immigrants may be a possible explanation. Another Dutch study performed in a multi-ethnic neighborhood of Rotterdam reported an equivalent prevalence of positive anti-HBc of 16%, weighted by sex and ethnicity. Interestingly, one-third of the patients with a positive anti-HBc was born in a low-endemic country. This illustrates that selective screening of high-risk patients for HBV is not effective. It should be noted however, that of the 21 patients with a positive HBV test result, eight were isolated anti-HBc positive. Of these patients, five were born in a non-endemic region. This raises the question whether these patients had a previous HBV infection with loss of measurable anti-HBs or a false-positive anti-HBc test result. Multiple diagnostic tests are available for testing anti-HBc and these different tests can show various outcomes within the same patient. According to a large Dutch study in donor patients, low-reactivity of an anti-HBc test in combination with undetectable anti-HBs and a Western European background suggests false positivity. In contrast, an isolated positive anti-HBc test in combination with a patient born in an endemic country (>2%) is a reason to assume a true test result and requires further action. As a result it is possible that the prevalence of patients with a history of HBV in our study cohort is overestimated. Interestingly, the age of patients with an isolated anti-HBc was significantly higher than the age of patients with both a positive anti-HBc and anti-HBs. Previous studies suggest that with increasing age, the decline in anti-HBs titers is the most likely explanation for an isolated anti-HBc result. This supports the conception that every patient with an isolated anti-HBc positive result should be considered as at risk for HBVr since it is difficult to be sure that it reflects a false-positive test result.

The key question of this study was to evaluate the result of implementation of the routine HBV screening protocol. Before introduction of the protocol, one HBVr occurred in our cohort and one patient was started on prophylactic antiviral therapy; after protocol implementation, no HBVr occurred and one patient was started on prophylactic antiviral therapy. Before introduction of the protocol, an anti-HBc prevalence of 21.6% was identified, while after implementation of the protocol the anti-HBc prevalence was 14.1%. This is explained by a selection effect: before the HBV screening protocol, a selection of patients was screened who were considered at-risk for HBV. However, without the HBV screening protocol, patients will be missed who are not directly identified as at-risk for HBV. In this study cohort, without the HBV screening protocol we would have missed four patients who tested anti-HBc positive at screening, because they were born in a non-endemic country and were not receiving high-risk medication, and therefore not considered as at-risk for HBV. Since the introduction of the protocol we had a standard follow-up protocol with liver serum transaminases and HBV-DNA to detect early signs of HBVr. A study investigating the cost-effectiveness of routine HBV screening in a hypothetical model of patients who start chemotherapy for solid tumors reports that it is not likely to be cost-effective. But the most recent guidelines of the Centers for Disease Control and Prevention, The American Association for the Study of the Liver and the European Association for the Study of the Liver all recommend...
universal screening despite not being cost-effective.\textsuperscript{2,9,12,13} Given the low costs of HBV screening, the high additional costs and clinical consequences for patients with HBVr, we recommend routine HBV screening for all patients receiving chemotherapy.\textsuperscript{17} In conclusion, the implementation of routine HBV screening for all patients treated with chemotherapy increases the number of patients identified as at-risk for HBVr and contributes to prevention of HBVr. The high prevalence of anti-HBc-positive patients in this study indicates the importance of routine HBV screening. To achieve a 100\% screening rate, patients must only be allowed to start chemotherapy when the HBV test results are known, for example with an automated warning system to check HBV status before chemotherapy prescription. A cultural change for routine HBV screening and knowledge about the existing guidelines will be a first step to increase the screening rate in patients treated with chemotherapy.

\textbf{ACKNOWLEDGEMENTS}

We wish to thank Mieke Vink-de Goeij and Frank Kristel for providing the database with all patients that received chemotherapy at the Medical Centre Slotervaart.

\textbf{DISCLOSURES}

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

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14. HBV Richtsnoer – Toepassbaarheid van de EASL richtlijn in de Nederlandse situatie. 2018;April (Versie 1.5).
CASE REPORT

Bizarre behavior and decreased level of consciousness in an adult patient

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ABSTRACT

This case report presents an adult patient with decreased levels of consciousness and bizarre behavior. A silent delirium was first suspected however, symptoms did not improve and further examination revealed elevated ammonia levels. A hepatic cause and portosystemic shunting were excluded and eventually a diagnosis of ornithine transcarbamylase deficiency was made. After treatment with high carbohydrate intake, a low protein diet and supplementation with arginine and sodium benzoate, the patient recovered.

KEYWORDS

Hyperammonemia, OTC deficiency, urea cycle

BACKGROUND

Ammonia is continuously produced by the breakdown of protein. It easily crosses the blood-brain barrier and is toxic for the brain when plasma concentrations are increased (> 45 µmol/l), causing a wide range of symptoms (table 1).¹² In the liver, ammonia is converted to water-soluble urea through the urea cycle after which it is excreted into the urine (figure 1).

Increased plasma ammonia concentrations develop when the liver cannot fully convert ammonia. In approximately 90% of adult cases, this is caused by liver failure.³ However, if there are no signs of liver failure, non-hepatic causes of hyperammonemia should be investigated, including increased production or decreased metabolism of ammonia.⁴⁻⁵ When ammonia production exceeds the liver’s capability to convert this to urea, plasma ammonia levels rise. For example, gastrointestinal bleeding, urease-producing bacteria and urinary tract diversion can cause increased ammonia production.⁴⁻⁵

Table 1. Symptoms of hyperammonemia¹²

<table>
<thead>
<tr>
<th>Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and vomiting</td>
</tr>
<tr>
<td>Confusion and strange behavior</td>
</tr>
<tr>
<td>Agitation</td>
</tr>
<tr>
<td>Slurred speech</td>
</tr>
<tr>
<td>Problems with coordination and balance</td>
</tr>
<tr>
<td>Seizures</td>
</tr>
<tr>
<td>Cerebral edema</td>
</tr>
<tr>
<td>Abnormal posture</td>
</tr>
<tr>
<td>Decreased conscious state</td>
</tr>
</tbody>
</table>

What was known on this topic?
Information about the pathogenesis and treatment of urea cycle defects is available. The disorder however, is very rare and thus not well known by general practitioners.

What does this add?
The answers will appear in a separate box in the text. This case report is an excellent example of the importance of keeping a broad differential diagnosis. This patient was first admitted to a general hospital and only upon extensive investigation the final and rare diagnosis was eventually identified.
Another mechanism is portosystemic shunting, where ammonia bypasses the liver, preventing conversion to urea. Medication has also been associated with elevated ammonia levels; for example, valproic acid can lead to hyperammonemia.

A rare cause of hyperammonemia in adults can be an inborn error of metabolism, e.g. hyperinsulinism-hyperammonemia syndrome or urea cycle defects (UCD). Defects in the urea cycle may lead to high ammonia levels, especially in catabolic states. Although these defects are genetic primarily affecting children, the disorder does require medical attention in adulthood in most patients. Urea cycle defects present with typical changes in plasma amino acid levels, depending on the defective enzyme.

**OBJECTIVE**

The objective of this case report is to increase awareness for rare inborn errors of metabolism in adults and measure ammonia levels in patients with unexplained episodes of decreased consciousness. After excluding more frequent causes for hyperammonaemia, a urea cycle defect should be considered and appropriately diagnosed.

**CASE REPORT**

A 54-year-old female presented at the emergency department with a fever and a gradually decreasing level of consciousness. Her medical history revealed no significant comorbidities. On physical examination, she was found to be disoriented and had a high fever. Laboratory tests revealed elevated ammonia levels.

To rule out other causes of hyperammonemia, a workup was performed which included a full metabolic panel and a urine sample for ammonia levels. The results were consistent with a urea cycle defect.

**Figure 1.** Urea cycle. A defect in ornithine transcarbamylase (OTC) results in low levels of citrulline and sometimes arginine and elevations in glutamine (activation of glutamine synthase adds an amino group to glutamate, which results in the formation of glutamine as a buffer; high levels of glutamine are a sensitive indicator of a urea cycle defect). The alternative pathway shows how sodium benzoate and sodium phenylacetate can lead to an alternative method of ammonia excretion.
of consciousness over several days. Her medical history included borderline personality disorder, depression, alcohol and benzodiazepine addiction, a gastric bypass 20 years ago and a recent doxycycline-induced pancreatitis, which had led to severe weight loss. Upon physical examination, she had a pulse of 118 beats per minute, blood pressure of 100/60 mmHg, oxygen saturation of 90% and a temperature of 38.5 degrees Celsius. A chest X-ray showed an infiltration of the left lower lobe, which led to the diagnosis of pneumonia. She was treated with intravenous antibiotics and a silent delirium was hypothesized. However, despite adequate treatment of the infection, she did not regain full consciousness and exhibited manipulative and bizarre behavior. Consulting a neurologist and an additional neurological examination, including a computed tomography (CT)-cerebrum, did not reveal a cause. Flumazenil treatment, 0.25 mg intravenously, for suspected benzodiazepine intoxication led to temporary improvement, followed by discharge from the hospital. However, one month later, the patient was readmitted, again with a decreased level of consciousness. Her vital signs, physical and routine laboratory examination were normal this time. She had lost seven kilograms over several weeks and had become severely malnourished. Neurologic examination was normal aside from a decreased score of E3M5V5 on the Glasgow Coma Scale (GCS). Urinary drug screening was positive for benzodiazepines, but repeated treatment with flumazenil was unsuccessful. A CT scan and magnetic resonance imaging of the brain were normal. During admission, the patient exhibited the same bizarre behavior as during the previous admission. She became extremely agitated, spoke incoherently or tried to manipulate the staff. The psychiatrist was consulted but could not explain the symptoms by delirium, conversion disorder or psychosis and suggested a somatic cause for the symptoms. Extended chemical laboratory investigations showed an increased plasma ammonia level of 157 µmol/l (range 10-45 µmol/l). This hyperammonemia explained the symptoms including the bizarre behavior. Initial treatment with lactulose was started immediately, leading to insufficient improvement. Further examination was aimed at finding the underlying cause for the increased plasma ammonia. The differential diagnosis included an intrahepatic cause or portosystemic shunting, especially since the patient had a history of alcohol addiction. However, laboratory analysis, ultrasound and liver biopsy did not show any signs of liver cirrhosis or fibrosis. Portosystemic shunting was excluded with duplex ultrasound and CT scan. After excluding the above-mentioned most common causes for hyperammonemia, a potential defect in the urea cycle was suspected. A specialized center, Amsterdam University Medical Center (location AMC), was consulted and plasma amino acids and urinary orotic acid levels were measured.

Table 2. Plasma amino acids

<table>
<thead>
<tr>
<th>Amino acid</th>
<th>µmol/l</th>
<th>Reference range µmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glutamine</td>
<td>1328</td>
<td>435-721</td>
</tr>
<tr>
<td>Ornithine</td>
<td>41</td>
<td>27-98</td>
</tr>
<tr>
<td>Citrulline</td>
<td>&lt; 5</td>
<td>16-46</td>
</tr>
<tr>
<td>Arginine</td>
<td>21</td>
<td>46-128</td>
</tr>
</tbody>
</table>

Glutamine levels were raised and citrulline and arginine levels were low (table 2).

These levels could be caused by a defect in the urea cycle but also could have been caused by the severe malnutrition. In both cases, adequate amino acid supplementation is necessary, but high protein feeding can aggravate a urea cycle defect. Therefore, we decided to treat the patient as appropriate for a urea cycle defect with intravenous glucose, high carbohydrate feeding with adequate amino acid supplementation including arginine, but general protein restriction and sodium benzoate. Sodium benzoate works as a nitrogen scavenger by promoting an alternative pathway for the excretion of ammonia (see figure 1).

After nourishment, laboratory tests showed persisting low citrulline levels and increased orotic acid in urine, pointing towards ornithine transcarbamylase (OTC) deficiency as the underlying cause of the hyperammonemia. Mutation analysis did not reveal a mutation in the OTC gene. The patient regained full consciousness, had a GCS score of E4M6V5 and could be discharged.

DISCUSSION

It is important to consider hyperammonemia when a patient has an unexplained altered conscious state. As discussed earlier, the most common cause is liver failure. If liver failure has been excluded, analysis for non-hepatic causes should be considered.

Urea cycle defects are rare and usually present in childhood, with an estimated incidence of 2-3 in 100,000.10-13 However, 20% of patients present after 12 years of age.4 OTC is the most common urea cycle defect and is an X-linked disorder primarily affecting males. Presumably, as a result of random X-inactivation, clinical features in females may vary from severe episodes of hyperammonemia to asymptomatic disease.14 OTC deficiency may remain undiagnosed, especially in carrier females and can become apparent under extreme catabolic stress. In this particular case, the extreme weight loss of seven kilograms in several weeks after pancreatitis probably provoked the metabolic derangement. It is known that in up to 20% of all cases, no disease-causing mutation can be established.14 Therefore, plasma amino acids and

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urinary orotic acid analysis are crucial for confirmation of the diagnosis and to discriminate from other urea cycle defects.

In conclusion, hyperammonemia is strongly suspicious of a urea cycle defect in the absence of known hepatic disease. Since hyperammonemia and high glutamine levels may result in cerebral edema and even death, patients with high ammonia levels should be immediately treated as having a UCD, pending further diagnostic testing on samples that have been collected prior to treatment.

DISCLOSURES

All authors declare no conflicts of interest. C.E.M. Hollak is involved in pre-marketing research with Genzyme, Protalix and Idorsia.

REFERENCES


CASE REPORT

Radiation-induced morphea: autoimmunity as a risk factor

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ABSTRACT

Radiation-induced morphea (RIM) is a rare complication of radiotherapy of unknown etiology. We report the case of a woman with a history of vitiligo and Hashimoto’s thyroiditis, who developed RIM following radiotherapy for breast carcinoma. We suggest that a history of autoimmune disease is a possible risk factor for the development of RIM.

KEYWORDS

Radiation-induced morphea, Hashimoto’s thyroiditis, vitiligo, radiotherapy complications, multiple autoimmune diseases, localized scleroderma

INTRODUCTION

Radiation-induced morphea (RIM) is a rare cutaneous complication of radiotherapy. Little is known about the predictive risk factors for the development of this condition. In an attempt to highlight the role of autoimmunity in the pathogenesis of the disease, we present a woman with Hashimoto’s thyroiditis and vitiligo, who developed a radiation-induced morphea after radiotherapy for breast carcinoma. To our knowledge, our case is the fourth report describing the association of morphea, Hashimoto’s thyroiditis and vitiligo, and the only one concerning the radiation-induced form of the condition.

OBSERVATION

A 60-year-old woman was diagnosed with breast carcinoma in 2012. She had a right breast mastectomy and an axillary node sampling. She received three cycles of adjuvant 5-Fluourouracil (500 mg/m²) and cyclophosphamide (500 mg/m²), followed by three cycles of docetaxel (100 mg/m²). Adjuvant chemotherapy was followed by radiation therapy to her chest wall for a total dose of 50 Gy, 2 Gy per fraction, at a rhythm of one fraction per day, five days per week. She was placed on tamoxifen. Additionally, she was examined for a Hashimoto’s thyroiditis and increased values of thyroid peroxidase antibodies were detected. Finally, she presented with extensive vitiligo that began at least 10 years ago, and was aggravated by radiotherapy, as described below (figure 1).

Four years ago, after radiotherapy was completed, the patient developed four asymptomatic sclerotic and atrophic well-circumscribed patches surrounded by lilac rings: one beyond the right inframammary area, in the right hypochondriac region; and three others on the left inframammary area, the abdomen and the thigh. Subsequent cutaneous biopsies demonstrated thickening and hyalinization of connective tissue of deep dermis, with perivascular and focal interstitial lymphocytic and plasma cell infiltrate. Laboratory investigations showed slightly positive antinuclear antibody test (1:80, speckled), but anti-SS-A/B, anti-Sm, anti-DNA and anti Scl 70 antibodies were all negative. Based on history, clinical presentation,

What was known on this topic?

Radiation-induced morphea is a rare complication of radiotherapy. Morphea differ from systemic sclerosis by lacking acrosclerosis, internal organ involvement, Raynaud’s phenomenon, and much less frequent appearance of autoantibodies.

What does this add?

History of autoimmune disease is a possible risk factor for the development of radiation-induced morphea.
laboratory and histopathological findings, we made a diagnosis of radiation-induced morphea. The patient was treated with ultrapotent topical corticosteroids, resulting in the complete abolishment of lesions in the inframammary regions and abdomen, although residual atrophy and depigmentation through koebnerization remained in the patch of the thigh (figure 2).

**DISCUSSION**

Morphea, also known as localized scleroderma, is a rare inflammatory skin disorder that affects the skin and sometimes underlying subcutaneous tissue, muscles or bones. Morphea is clinically different from systemic sclerosis in that it lacks acrosclerosis, internal organ involvement and Raynaud’s phenomenon. Furthermore, antinuclear antibodies are detected in more than 85% to 95% of patients with systemic sclerosis, but are not a prominent feature of morphea. Morphea has been recognized as a complication of radiotherapy since the 1990s, mostly for breast cancer patients. Like the patient described above, it can develop several years after radiation therapy. To our knowledge, the disease has never been associated with autoimmunity. It is still unclear why RIM develops in some individuals. The strongest hypothesis proposes that antigens from altered endothelial cells, fibroblasts and collagen induce an immune response. This results in cytokine and growth factor production that stimulates the excessive creation of collagen. This reaction seems to be enhanced by the history of autoimmunity in our patient. The extended delay in disease onset may be due to a cross-reactive immune response against radiation-induced antigens and some subsequent infections that occur several years later.

In this observation, radiation-induced morphea arose in a middle-aged woman, similar to most autoimmune diseases, in which a clear sex difference is observed. In addition, our patient’s condition was preceded by vitiligo and Hashimoto’s thyroiditis for several years, and the role of autoimmunity is well documented for these associated diseases. Although not yet fully elucidated, autoimmunity is increasingly perceived as the underlying cause in the development of “spontaneous morphea”. This relationship is justified by three points: the association of some cases of morphea with an increased level of antinuclear antibodies; the familiar clustering of morphea and the coexistence of the morphea with multiple autoimmune syndromes. Morphea has been reported in association with Hashimoto’s thyroiditis and vitiligo in three cases. This particular case shows that radiation-induced morphea, like spontaneous morphea, can be associated to Hashimoto’s thyroiditis and vitiligo.

Treatment may prevent further progression of the disease but is not fully effective in reversing all disease damage;
therefore, patients at risk of developing the morphea must be monitored, and early intervention is needed to prevent scaring.

**CONCLUSION**

No risk factors for the development of RIM are known to date, but we believe that a patient with a previous autoimmune disease treated with radiotherapy is at high risk for developing morphea. Hence, physicians should take extra precautions and treat the disease early to prevent unnecessary scaring.

**DISCLOSURES**

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

**REFERENCES**

ALL GOOD THINGS COME IN THREES

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CASE REPORT

A 67-year-old female visited the outpatient clinic because of a low-grade fever and abdominal pain. Her medical history was relevant for undifferentiated connective tissue disease (UCTD) and ureteropelvic junction obstruction. At the time, no diagnosis was made and she was sent home. However, after three days, she was admitted to our hospital because of fever and suspected sepsis. Upon admission, she was hemodynamically stable and laboratory investigation revealed a leucocytosis of 9 x 10^9/l, an elevated C-reactive protein (CRP) of 163 mg/l and a preserved kidney function with a creatinine of 75 μmol/l. Urinalysis revealed pyuria and ultrasound was consistent with hydronephrosis. She was diagnosed with sepsis due to pyonefrosis, and drainage of the pyelum was secured with a nephrostomy and she was started on Ceftazidime. Unfortunately, she developed an anaphylactic reaction, including facial swelling and angioedema for which she was admitted to the ICU and intubated. She was treated with antihistamines, steroids and adrenalin and Ceftazidime was discontinued. Amongst her medication were hydroxychloroquine and low-dose prednisone.

During her stay in intensive care, three dissimilar skin lesions were observed as shown in figure 1 (1A, ankle; 1B, fingers and 1C, buttocks). The dermatologist was consulted and a biopsy was performed from the lesion on the pelvis (figure 1C). Cryoglobulins were only slightly elevated. Three separate diagnoses were considered.

WHAT IS YOUR DIAGNOSIS?

See page 33 for the answer to this photo quiz.

Figure 1. Three skin lesions: A: ankle; B: fingers; C: buttocks
DIAGNOSIS

In our patient, three dissimilar skin lesions were present during a septic episode. On her ankle, a classical ecthyma gangrenosum lesion was observed. This lesion is pathognomonic for Pseudomonas Aeruginosa bacteremia and indeed, blood and urine cultures from this patient grew Pseudomonas Aeruginosa. Due to hematogenous spread, the organism invades the arteries and veins in the dermis and subcutaneous tissues leading to vasculitis and necrosis. Ecthyma gangrenosum lesions are commonly seen on the legs and are predominantly present in immunocompromised patients. Secondly, purple maculae were observed on her fingers. A previous report on patients with a few of these so called “nail fold lesions” has been published and these lesions are known to co-exist with rheumatoid arthritis/UCTD and are a sign of occlusive vasculitis. However, during this septic episode, the size and number of her nail fold lesions severely increased, which was interpreted as a local exacerbation of autoimmune associated occlusive vasculitis as a result of generalized systemic immune activation during sepsis. In addition, purpura were observed on her buttocks. However, in this case, the numerous and spread out lesions did not appear to be necrotic and were not consistent with the ecthyma lesion we observed on her ankle. A biopsy was taken and showed a granulocytic infiltration consistent with a leucocytoclastic vasculitis. No thrombi or necrosis were observed. Leucocytoclastic vasculitis is also known as “hypersensitivity vasculitis” and is most often idiopathic. It usually results from deposition of immune complexes at the vessel wall, although non-immune complex mediated mechanisms may be involved as well. There are many other triggers including, but not limited to, sepsis, infections, neoplasms, inflammatory disorders, and drugs.

Taken together, in this case several vasculitis skin eruptions appeared together during sepsis and in threes: an infectious necrotic vasculitis (ecthyma) on the ankle, an exacerbation of pre-existent occlusive autoimmune-related nail fold lesions and the occurrence of a cutaneous small vessel leucocytoclastic vasculitis near the buttocks. After several days of antibiotic treatment for Pseudomonas Aeruginosa, all three forms of skin lesions rapidly resolved indicating that the treatment of bacteremia as well as the decrease in systemic inflammatory activation may be all that is required to treat these skin abnormalities.

REFERENCES

PHOTO QUIZ

Garland triad identified with HRCT

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CASE REPORT

A 33-year-old female of south Indian origin presented with a history of low-grade fever, migratory polyarthralgia with redness and swelling in her legs. On examination, there were erythematous, tender, immobile nodules over both of her shins. The remainder of her general and systemic examination were unremarkable. Her investigation revealed elevated serum angiotensin converting enzyme (ACE) level along with a non-reactive Tuberculin skin test and negative quantiFERON-TB Gold (QFT). High resolution computed tomography (HRCT) of the chest revealed a combination of right paratracheal nodes (figure 1, orange arrow), right hilar nodes (figure 1, yellow arrow) and left hilar nodes (figure 1, green arrow). Identify this sign, which is very typical of a particular condition and described by chest X-ray.

WHAT IS THE DIAGNOSIS?

See page 35 for the answer to this photo quiz.
DIAGNOSIS

Lofgren syndrome is described as a combination of erythema nodosum (EN), hilar adenopathy, migratory polyarthralgia and fever, and is seen primarily in women. HRCT of the chest revealed a combination of right paratracheal nodes (figure 1, orange arrow), right hilar nodes (figure 1, yellow arrow) and left hilar nodes (figure 1, green arrow) which is exactly like the garland triad seen on the chest X-ray. Garland triad, also known as the 1-2-3 sign or Pawnbrokers sign is a pattern typical, but not specific, of sarcoidosis and identified by chest X-ray.\(^1\,^2\) As intrathoracic adenopathy is better visualised on HRCT than conventional radiograph, a garland triad can be better identified with HRCT, hence reducing the number of false negative reports.

REFERENCES

PHOTO QUIZ

Progressive dyspnea

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CASE REPORT

A 22-year-old male presented to the emergency department with progressive dyspnea, cough, episodes of fever and chest pain. There was no history of vomiting or extensive alcohol intake or trauma. His medical history included asthma and the use of cannabis and MDMA (commonly known as ecstasy). On physical examination, the patient was tachypnoeic and his oxygen saturation was 90% in ambient air. His chest sounds were normal and there were no cardiac murmurs. Laboratory results yielded normal leucocytes, a C-reactive protein of 235 mg/l, elevated creatine kinase and lactate dehydrogenase levels of 326 U/l and 453 U/l, respectively with normal cardiac enzymes. An echocardiogram was significant for a sinus tachycardia with normal conduction times but repolarisation abnormalities in leads V2 to V6. A chest X-ray was performed (figure 1).

WHAT IS YOUR DIAGNOSIS?

See page 37 for the answer to this photo quiz.

Figure 1. An X-ray showing subcutaneous emphysema (upper red arrow); a pneumomediastinum can also be seen (lower red arrow)

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DIAGNOSIS

Spontaneous pneumomediastinum or Hamman’s syndrome

The chest X-ray revealed subcutaneous emphysema and a pneumomediastinum (figure 1). Computed tomography confirmed an extensive pneumomediastinum as well as subcutaneous emphysema together with ground glass opacities (figure 2). There were no signs of esophageal rupture. Echocardiography showed air artefacts around the pericardium.

Hamman’s syndrome is named after Louis Hamman and describes subcutaneous emphysema in association with a spontaneous pneumomediastinum. Pneumomediastinum can be categorized as a primary or spontaneous pneumomediastinum and a secondary pneumomediastinum. There is no obvious cause for a spontaneous pneumomediastinum, whereas trauma or injury is the underlying cause of a secondary pneumomediastinum. A primary pneumomediastinum is a rare phenomenon with an incidence of approximately 1 in 25,000 and predominantly affects males, and several mechanisms are described to explain its development. A sudden increase in alveolar pressure due to coughing can cause a rupture of the alveolar wall causing air to leak through the surrounding bronchovascular sheath. Air trapping, similar to asthma, also contributes to the development of high alveolar pressure. Apart from barotrauma, weakening of the alveolar wall can contribute to the occurrence of a pneumomediastinum. Viral pneumonitis also causes the alveolar walls to weaken, as do the use of drugs, such as cannabis and MDMA. Our patient was diagnosed with Influenza type A, suffered from asthma and was known to use both cannabis and MDMA.

REFERENCES

LETTER

Exercise-induce anaphylaxis, food-dependent exercise-induce anaphylaxis, cholinergic urticaria and Kounis syndrome

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Anaphylaxis is a condition that occurs unexpectedly. It creates fear and uncertainty to both physicians and the public and may progress rapidly in patients of all ages, in both sexes and often in young and otherwise healthy individuals. Exercise-induced anaphylaxis (EIA) is a rare, unpredictable and potentially fatal form of anaphylaxis, which is more common in atopic individuals, and associated with physical activity or exercise. EIA may occur independently of food allergen ingestion, and for a sub-population of patients, both ingestion of a food allergen either pre- or post-exercise and exercise are required to induce food-dependent exercise-induced anaphylaxis (FDEIA).

Such an interesting FDEIA case was published recently in the Netherlands Journal of Medicine. The authors report on a 49-year-old male with no cardiovascular disease history, who experienced a previous episode of urticaria during a strenuous cycling trip. This patient also developed anaphylactic shock during physical exercise, that was accompanied by urticaria on his chest and arms, abdominal pain, vomiting and diarrhea. Electrocardiogram and laboratory findings were suggestive of acute ST-elevation myocardial infarction. This case raises important issues concerning the pathophysiology of exercise, food consumption, allergy, anaphylactic shock, cholinergic, stress-induced, allergy to effort, aquagenic urticaria and the Kounis hypersensitivity-associated acute coronary syndrome.

Indeed, during exercise the following can occur:

1. Mast cell degranulation is facilitated during exercise due to a decrease in pH resulting in an acidic environment.

2. Tissue transglutaminase enzyme alterations occur during exercise that may cause peptide aggregation, which in turn, increases IgE cross-linking.

3. A sudden redistribution of blood during exercise transports allergens away from the gut to the skin and/or skeletal muscle, where phenotypically different mast cells reside.

4. Exercise applies an inhibitory effect on gastric acid secretion. This decreases digestion of oral allergens and preserves the structural integrity of the gastrointestinal duct, which leads to continued systemic absorption of the allergens whether it be profilins, lipid transfer proteins or other antigenic determinants.

5. During food intake, substances such as alcohol can damage the ultrastructure of gastric and gut mucosa and induce alterations in their integrity and permeability; these result in endotoxins entering the circulation and could potentially facilitate allergen entry.

6. Experiments have shown that during exercise, plasma osmolarity is raised and this can increase basophil activation and histamine release.

FDEIA has been associated with several causes including disease conditions; environmental factors; foods such as fruits, fish, nuts and vegetables; and drugs. These should be always tested for, in order to identify the culprit. Wheat and tomatoes are commonly used food items that can induce exercise anaphylaxis and should also always be considered.

The described patient was suspected, correctly, to have suffered EIA provoked by wheat; the patient developed EIA after eating wheat before his cycling trip. The authors also wanted to conduct a food-exercise challenge, however the patient had accidently challenged himself by eating...
bread and dancing before arriving at the hospital. To our knowledge, FDEIA has been associated with acute coronary syndrome and in particular, with the Kounis hypersensitivity-associated acute coronary syndrome only once in the past.9

This patient developed urticaria on his chest and arms, abdominal pain, vomiting and diarrhea after warming up the patient’s body temperature, however his condition deteriorated and he developed angioedema and collapsed. There is controversy whether peripheral vasodilatation or coronary vasoconstriction is the main cause of anaphylactic cardiovascular collapse.10-11 Whereas electrocardiography, cardiac enzymes and troponin were suggestive of myocardial injury, echocardiography did not show any wall abnormalities, and thus excluded takotsubo cardiomyopathy (also known as stress cardiomyopathy). Ideally, coronary angiography would have resolved this problem, had it been recommended.

Systemic manifestations such as abdominal pain, nausea, vomiting and diarrhea associated with effort-induced urticaria are characteristics of so-called cholinergic urticaria, also known as stress urticaria, allergy to effort and aquagenic urticaria. Cholinergic urticaria is a type of physical urticaria characterized by a number of short-lasting, highly pruritic wheals resembling the wheals depicted in the paper by Rosier et al.1

This kind of urticaria has been attributed to water in sweat (aquagenic) during exercise, which reacts with sebum, forming a compound acting as an allergen that induces the release of histamine.12

Effort-induced anaphylaxis associated with allergy and myocardial infarction seem to constitute a clinical complex that needs careful attention and should be always considered. Recognition, diagnosis, prevention and treating this complex is of paramount importance.

DISCLOSURES

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

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