Abstract

Vasculitis affecting the peripheral nerves predominantly manifests as subacute, progressive, asymmetric sensorimotor polyneuropathy or mononeuritis multiplex, and more rarely as painful mononeuropathy, pure sensory neuropathy, neuropathy of the cranial nerves, plexopathy, or as autonomic neuropathy. Vasculitic neuropathy may occur isolated or non-isolated (systemic) together with involvement of other organs. Systemic vasculitis with involvement of the peripheral nerves is further subdivided into primary (Takayasu syndrome, giant cell arteritis, classical panarteritis nodosa, thrombangitis obliterans, Kawasaki disease, Churg-Strauss syndrome, Wegener granulomatosis, cryoglobulinemic vasculitis, Behcet’s disease, microscopic polyangiitis, Schoenlein Henoch purpura) (Table 1), or secondary as a complication of an autoimmune connective tissue disorder, infection, sarcoidosis, malignancy, medication, radiation, or diabetes (Table 2) (Gorson 2007). The course of systemic and non-systemic vasculitic neuropathy may be chronic relapsing, chronic progressive, or monophasic (Schaublin et al., 2005). Vasculitis of the PNS may be classified upon affection of the cranial or spinal nerves, upon affection of motor, sensory, autonomic fibers, or a mixture of these, upon affection of a single or several nerves, affection of small or larger arteries, or upon occurrence of vasculitis with or without involvement of other organs (Table 2). This review aims to give an overview on the current knowledge about the pathogenesis, clinical presentation, diagnosis, treatment, and prognosis of vasculitic neuropathy.

Pathogenesis

Involvement of the PNS in systemic vasculitis results from infiltration of the vasa nervorum or the epineural arteries by inflammatory cells (Pagnoux and Guillevin 2005). Infiltration of the vascular wall facilitates thrombosis and consecutive ischemia. The infiltration is facilitated by breaches in the blood-nerve barrier, which is not as effective as the blood brain barrier. Damage to the blood-nerve barrier is induced by proinflammatory cytokines, oxidative stress-derived molecules, or metalloproteinases (Pagnoux and Guillevin 2005). Pathologic data are supportive of a primary T-cell mediated immune-pathogenesis (Collins and Periquet, 2004). Altered expression or function of adhesion molecules or
leukocyte or endothelial cell activation seem to play a key role in the development of the inflammatory process (Schaublin et al., 2005). The role of anti-neutrophil cytoplasmic antibodies (ANCA) in the pathogenesis of vasculitic neuropathy is unclear (Pagnoux and Guillevin, 2005). Pain in vasculitic neuropathy is believed to be induced by the neurotrophic growth factor, which can be effectively transferred to sensory axons (Yamamoto et al., 2003).

**Clinical presentation**

The most frequent manifestations of PNS vasculitis are asymmetric, axonal, sensorimotor polyneuropathy (PNP) of acute or subacute onset or progressive, painful multiple mononeuropathy (mononeuritis multiplex), mononeuropathy, pure sensory neuropathy (Seo et al., 2004), plexopathy, cranial neuropathy, or autonomic neuropathy (Gorson 2007; Zivkovic et al., 2007; Burns et al., 2007; Vrancken et al., 2007; Gulturk et al., 2008). More than 50% of the patients present with axonal, sensorimotor PNP (Zivkovic et al., 2007; Oka et al., 2007). Up to 30% of the cases present with mononeuritis multiplex (Zivkovic et al., 2007). A small number of patients (16%) presents with pure sensory abnormalities (Seo et al., 2004; Chao et al., 2007). The prevalence of the other presentations is unknown. The clinical manifestations of vasculitis vary not only between the types of vasculitis but also within an entity (Table 3). Although any nerve can be affected, most patients have initial symptoms in the tibial or peroneal divisions of the sciatic nerve (Schaublin et al., 2005). In quite a number of patients symptoms are dominated by pain. In about one third of the patients neuropathy is the first and only manifestation of necrotizing vasculitis (Said et al., 2003). In the following sections non-systemic vasculitis of the PNS and systemic vasculitis involving the PNS are described in more detail.

**Systemic vasculitis**

**A. PRIMARY SYSTEMIC VASCULITIS**

1. **Large vessel vasculitis**

Giant cell arteritis

PNS affection is an uncommon but sometimes life-threatening manifestation of giant cell arteritis (Pfädenhauer et al., 2007). Affected patients present with subacute sensorimotor deficits in a cervico-brachial plexus distribution (Pfädenhauer et al., 2007). Compared with stroke or neuro-ophthalmologic complications in giant cell arteritis, PNS involvement in form of vasculitic neuropathy is much rarer (Pfädenhauer et al., 2007).

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**Table 1**

Nomenclature of primary systemic vasculitis according to the Chapel Hill Consensus Conference depending on the size of the affected vessels (modified, additionally included were thrombangitis obliterans and M. Behcet)

<table>
<thead>
<tr>
<th>Large vessel vasculitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giant cell arteritis</td>
</tr>
<tr>
<td>Granulomatous arteritis of the aorta and its major branches, particularly the extracranial branches of the carotid arteries, usually in patients &gt; 50 y, and associated with polymyalgia rheumatica</td>
</tr>
<tr>
<td>Takayasu arteritis</td>
</tr>
<tr>
<td>Granulomatous arteritis of the aorta and its major branches, usually affecting patients &lt; 50 y</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medium-sized vessel vasculitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic panarteritis nodosa</td>
</tr>
<tr>
<td>Necrotizing vasculitis of the medium- or small-sized arteries</td>
</tr>
<tr>
<td>Thrombangitis obliterans (Buerger’s disease)</td>
</tr>
<tr>
<td>Kawasaki syndrome</td>
</tr>
<tr>
<td>Granulomatous vasculitis of large, medium, or small sized arteries, frequently affecting the coronaries, enlarged lymph nodes, usually in children</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Small vessel vasculitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Churg-Strauss syndrome</td>
</tr>
<tr>
<td>Wegener’s granulomatosis</td>
</tr>
<tr>
<td>Cryoglobulinemic vasculitis</td>
</tr>
<tr>
<td>Behcet’s disease</td>
</tr>
<tr>
<td>Microscopic polyangitis</td>
</tr>
<tr>
<td>Schoenlein-Henoch purpura</td>
</tr>
<tr>
<td>Cutaneous leukocytoklastic vasculitis</td>
</tr>
</tbody>
</table>

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**Clinical presentation**

The most frequent manifestations of PNS vasculitis are asymmetric, axonal, sensorimotor polyneuropathy (PNP) of acute or subacute onset or progressive, painful multiple mononeuropathy (mononeuritis multiplex), mononeuropathy, pure sensory neuropathy (Seo et al., 2004), plexopathy, cranial neuropathy, or autonomic neuropathy (Gorson 2007; Zivkovic et al., 2007; Burns et al., 2007; Vrancken et al., 2007; Gulturk et al., 2008). More than 50% of the patients present with axonal, sensorimotor PNP (Zivkovic et al., 2007; Oka et al., 2007). Up to 30% of the cases present with mononeuritis multiplex (Zivkovic et al., 2007). A small number of patients (16%) presents with pure sensory abnormalities (Seo et al., 2004; Chao et al., 2007). The prevalence of the other presentations is unknown. The clinical manifestations of vasculitis vary not only between the types of vasculitis but also within an entity (Table 3). Although any nerve can be affected, most patients have initial symptoms in the tibial or peroneal divisions of the sciatic nerve (Schaublin et al., 2005). In quite a number of patients symptoms are dominated by pain. In about one third of the patients neuropathy is the first and only manifestation of necrotizing vasculitis (Said et al., 2003). In the following sections non-systemic vasculitis of the PNS and systemic vasculitis involving the PNS are described in more detail.

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### Table 2
Conditions associated with vasculitis of the peripheral nervous system

<table>
<thead>
<tr>
<th>Disorder</th>
<th>FPI</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systemic vasculitis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. Primary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Giant cell arteritis</td>
<td>Rare</td>
<td>(Pfadenhauer et al., 2007; Fineles and Arnold, 2007)</td>
</tr>
<tr>
<td>Classical panarteritis nodosa</td>
<td>35-75%</td>
<td>(Schaublin et al., 2005; Kostina-O’Neil et al., 2007)</td>
</tr>
<tr>
<td>Thrombangitis obliterans (Buerger disease)</td>
<td>Rare</td>
<td>(Vincent et al., 1985)</td>
</tr>
<tr>
<td>Kawasaki syndrome</td>
<td>1 patient</td>
<td>(Hicks et al., 1982)</td>
</tr>
<tr>
<td>Churg-Strauss syndrome</td>
<td>65-80%</td>
<td>(Zwerina et al., 2008; Djukic et al., 2008)</td>
</tr>
<tr>
<td>Wegener granulomatosis</td>
<td>14-50%</td>
<td>(Schaublin et al., 2005; Feuerlein et al., 2008)</td>
</tr>
<tr>
<td>Cyroglobulinemia</td>
<td>30-70%</td>
<td>(Schaublin et al., 2005; Cacoub et al., 2008)</td>
</tr>
<tr>
<td>M. Behcet</td>
<td>20%</td>
<td>(Gulturk et al., 2008)</td>
</tr>
<tr>
<td>Microscopic polyangitis</td>
<td>6-70%</td>
<td>(Schaublin et al., 2005)</td>
</tr>
<tr>
<td>Schönlein-Henoch purpura</td>
<td>Rare</td>
<td>(Bulun et al., 2001; Ohnuma et al., 2008)</td>
</tr>
<tr>
<td><strong>B. Secondary</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Mixed connective tissue disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>27%</td>
<td>(Servioli et al., 2007; Shoshtary et al., 2005)</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>50%</td>
<td>(Schaublin et al., 2005; Muramatsu et al., 2008)</td>
</tr>
<tr>
<td>Sjögren syndrome</td>
<td>45%</td>
<td>(Terrier et al., 2007; Iopate Lopate et al., 2006)</td>
</tr>
<tr>
<td>2. Infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>Unknown</td>
<td>(Said and Lacroix, 2005; Cacaoub et al., 2008)</td>
</tr>
<tr>
<td>Streptococcal infection</td>
<td>Unknown</td>
<td>(Traverso et al., 1997)</td>
</tr>
<tr>
<td>HIV</td>
<td>&lt; 1%</td>
<td>(Schaublin et al., 2005)</td>
</tr>
<tr>
<td>Cytomegaal virus</td>
<td>Rare</td>
<td>(Schaublin et al., 2005)</td>
</tr>
<tr>
<td>Histoplasmosis</td>
<td>Rare</td>
<td>(Berry et al., 1999)</td>
</tr>
<tr>
<td>Lues</td>
<td>Rare</td>
<td>(Mathew et al., 2007)</td>
</tr>
<tr>
<td>3. Sarcoioids</td>
<td>47%</td>
<td>(Said and Lacroix, 2005; Vital, 2008; Allen et al., 2003)</td>
</tr>
<tr>
<td>4. Medication</td>
<td>Rare</td>
<td>(Schapira et al., 2008)</td>
</tr>
<tr>
<td>5. Malignancy</td>
<td>32%</td>
<td>(Schaublin et al., 2005; Fain et al., 2007)</td>
</tr>
<tr>
<td>6. Radiation</td>
<td>1 patient</td>
<td>(Rubin et al., 2001)</td>
</tr>
<tr>
<td>7. Diabetic/non-diabetic plexopathy</td>
<td>Not applicable</td>
<td>(Schaublin et al., 2005; Said and Lacroix, 2005)</td>
</tr>
<tr>
<td><strong>Non-systemic vasculitis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Non-systemic vasculitis</strong></td>
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</tbody>
</table>

FPI: frequency of PNS involvement.

### Table 3
Frequent clinical presentations of neuropathy in some types of primary systemic vasculitis

<table>
<thead>
<tr>
<th></th>
<th>smPNP</th>
<th>MonMP</th>
<th>MoNP</th>
<th>CN</th>
<th>sNP</th>
<th>aNP</th>
<th>Plexopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCA</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>PAN</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombangitis</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kawasaki</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSS</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wegener</td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyroglobulinaemia</td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behcet</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Microscopic polyangitis</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schoenlein Henoch</td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

2. **Medium vessel vasculitis**

Classical panarteritis nodosa

Classical PAN is a rare systemic vasculitis of the small or medium-sized arteries without affection of arterioles, capillaries, or venules, affecting all organs (Schaublin et al., 2005; Harada et al., 2000). Viruses or bacteria, particularly streptococcus and hepatitis B, are assumed to be implicated in the pathogenesis of the disease. PAN is the systemic vasculitis most frequently associated with viral infection, particularly with hepatitis-B virus. One third to one half of the cases are associated with hepatitis B (Schaublin et al., 2005). In up to 75% of the patients with classical PAN vasculitic neuropathy occurs (Schaublin et al., 2005). Thus, classical PAN is one of the types of systemic vasculitis most frequently associated with vasculitic neuropathy. In cases of PNS involvement, patients present with painful mononeuritis multiplex (Hagiwara et al., 2003) or sensory ataxic neuropathy (Harada et al., 2000). In single cases the presentation may mimic chronic inflammatory demyelinating PNP (CIDP) (Tanaka et al., 1998).

Buerger’s disease (thrombangitis obliterans)

Thrombangitis obliterans is characterized by vasculitis of the small and medium-sized arteries of the lower arms and the lower legs. Men are more frequently affected than women. Involvement of the cerebrum, intestines, or the heart is rare. The typical finding of necrotizing vasculitis, fibrinoid necrosis, is absent in thrombangitis obliterans. In a single patient ischemic optic neuropathy has been reported as a manifestation of the disease (Coppeto and Adamczyk 1988). In another patient microvasculitis of nerve and muscle have been observed (Vincent et al., 1985).

Kawasaki disease

Kawasaki disease is an acute, self-limiting vasculitis of unknown etiology. The intense inflammatory process has a predilection for the coronary arteries (Wood and Tulloh 2008). Only in a single patient Kawasaki disease was associated with sensorimotor PNP (Hicks et al., 1982). Whether PNP in this patient was due to vasculitis or of other origin remains speculative.

3. **Small vessel vasculitis**

Churg-Strauss syndrome

Churg-Strauss syndrome (CSS) is a systemic, granulomatous vasculitis of the small and medium-sized arteries, arterioles, capillaries, or venules, characterized by infiltration of eosinophils. At onset patients present with asthma, allergic rhinitis, fever, or eosinophilia. They later develop eosinophilic infiltrates in the lung and the intestines, followed by systemic vasculitis. ANCA are elevated in some of the patients (Zwerina et al., 2008). Involvement of the PNS occurs in 65–80% of the cases (Schaublin et al., 2005) and usually manifests as mononeuritis multiplex, pure sensory neuropathy, or may progress into axonal sensorimotor PNP in the later stages (Chao et al., 2007; Hattori et al., 1999). In a study on 26 patients with CSS 15 (58%) developed vasculitic neuropathy (Cattaneo et al., 2007). Vasculitic neuropathy in these patients occurred earlier and was more severe than in patients with Wegener’s granulomatosis (Cattaneo et al., 2007). Children have less frequently vasculitic PNP than adults (Zwerina et al., 2008). In half of the patients vasculitis is histologically of the necrotizing type (Hattori et al., 1999). Because of the high prevalence of vasculitic neuropathy in CSS, it is one of the diagnostic criteria for CSS.

Wegener granulomatosis

Wegener granulomatosis is a systemic, necrotizing vasculitis of the capillaries, arterioles, or venules associated with granuloma formation in the upper and lower respiratory tract (Schaublin et al., 2005). About 80% of the patients develop glomerulonephritis, but principally each organ can be affected. c-ANCA are usually elevated. Vasculitis neuropathy occurs in about one third of the patients (14–40%) (Schaublin et al., 2005). In a cohort study on 26 patients with Wegener’s granulomatosis 6 (23%) developed vasculitic neuropathy (Cattaneo et al., 2007). Most frequently vasculitic neuropathy manifests as mononeuritis multiplex (Cattaneo et al., 2007) or rarely as mononeuropathy of a cranial nerve (Marsot-Dupuch et al., 2002) or sensorimotor PNP (Dickey and Andrews, 1990). Vasculitic neuropathy is usually less severe than in patients with CSS (Cattaneo et al., 2007). Neuropathy may be even the initial manifestation of the disease (Pleasure, 2001). Vasculitic neuropathy in patients with Wegener’s granulomatosis is of the axonal type (Jimenez-Medina and Yablun 1992). Usually, neuropathy develops within 2 y of diagnosis (Schaublin et al., 2005).

Cryoglobulinemia

Elevated cryoglobulin levels may develop secondary to chronic infection, autoimmune disease (in 16% of patients with rheumatoid arthritis) (Said and Lacroix, 2005), or hematologic disease (Schaublin et al., 2005). Cryoglobulinemia either remains asymptomatic or causes immune-complex mediated systemic vasculitis, mainly affecting the small
vessels and less frequently the medium-sized vessels (Cacoub et al., 2008, Saadoun et al., 2007). Cryoglobulinemia is associated with the proliferation of B-cell clones, which produce pathogenic IgM with rheumatoid factor activity (Saadoun et al., 2007). Clinical manifestations range from the mixed cryoglobulinemia syndrome (purpura, arthralgia, asthenia) to more serious manifestations with cutaneous, rheumatological (synovial), renal, or neurological manifestations (Saadoun et al., 2007; Alpa et al., 2008, Tada et al., 2004). Neurologic manifestations predominantly affect the PNS (Saadoun et al., 2007) and include painful sensorimotor PNP, pure sensory neuropathy, or mononeuritis multiplex (Schaublin et al., 2005; Saadoun et al., 2007). The most frequent distribution is distal sensory or sensorimotor PNP (Saadoun et al., 2007). Blood chemical examination may show elevated titers of antibodies against HCV, or anti-neuronal antibodies (anti-GM1 ganglioside or anti-sulfatide antibodies). Elevation of these antibodies is associated with evidence of active PNP (Alpa et al., 2008). Traditionally, it was thought that deposits of cryoprecipitable immune complexes in the vasa nervorum cause ischemic damage of axons. The strong association between severity of PNP and the titers of GM1 and anti-sulfatide antibodies, however, suggests that these antibodies could directly trigger axonal damage (Alpa et al., 2008). Symptomatic vasculitis is associated with old age, prolonged duration of infection, and high levels of type II IgM kappa cryoglobulins (Cacoub et al., 2008). Mixed cryoglobulins (type I and type II) can be found in > 80% of the patients with HCV (Saadoun et al., 2007; Joshi et al., 2007). Between 73 and 90% of the HCV positive patients develop cryoglobulinemia (Schaublin et al., 2005; Nemni et al., 2003). Less frequently cryoglobulinemia is associated with lymphoma. Risk factors to develop cryoglobulinemia are
female gender, alcohol intake > 50 g/d, liver fibrosis, and steatosis hepatitis (Cacoub et al., 2008).

Behcet’s disease

Behcet’s disease is a rare multisystem vasculitis of unknown origin affecting the central nervous system in only 5% of the cases (Turker et al., 2006) but the PNS in up to 20% of the cases (Akbulut et al., 2007; Atasoy et al., 2007). Clinically, patients with PNS involvement present with mononeuropathy, mononeuritis multiplex, sensorimotor PNP, or pure sensory PNP (Atasoy et al., 2007). Sensory fibers are more dominantly affected than motor fibers (Akbulut et al., 2007). PNS involvement may occur subclinically (Akbulut et al., 2007). Often there is involvement of the autonomic nerves, as confirmed by delayed sympathetic skin responses (Gulturk et al., 2008).

Microscopic polyangitis

Microscopic polyangitis is a subtype of panarteritis nodosa with the difference that it affects only small arterioles, capillaries, or venules (Schaublin et al., 2005). Microscopic vasculitis is one of those subtypes most frequently associated with vasculitic neuropathy. Up to 50% of the patients with microscopic polyangitis develop vasculitic neuropathy (Schaublin et al., 2005). Microscopic polyangitis is associated with elevated ANCA.

Schönlein-Henoch purpura

Schönlein-Henoch purpura represent a multisystem vasculitis with occasional involvement of the CNS, manifesting as headache, seizures, ataxia, or altered mental state. Only rarely the PNS is involved in form of mononeuropathies, mononeuritis multiplex, or PNP (Bulun et al., 2001; Mutsukura et al., 2007; Ohnuma et al., 2008).

B. Secondary systemic vasculitis

1. Connective tissue diseases

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune, multi-system disorder with neurological involvement, most commonly manifesting as cerebral vasculitis, transverse myelitis, or vasculitic PNP (Iliniczky et al., 2007). In a large cohort study on 670 consecutive SLE patients the prevalence of vasculitis was 11% (Ramos-Casals et al., 2006). The vast majority of these patients (86%) had small vessel vasculitis and only 14% had medium-sized vasculitis (Ramos-Casals et al., 2006). CNS involvement is much more frequent than PNS involvement and has been reported to occur in up to 75% of the cases (Rafai et al., 2007). PNS involvement includes classical symmetric PNP, mononeuropathies, or cranial nerve affection (Rafai et al., 2007). In 37% the autonomic nervous system may be affected. Usually, anti-phospholipid antibodies are high (Rafai et al., 2007). Patients with medium-sized vasculitis more frequently develop vasculitic neuropathy than patients with small-vessel vasculitis (Ramos-Casals et al., 2006).

Juvenile idiopathic arthritis

Juvenile idiopathic arthritis is an inflammatory disorder of unknown etiology, affecting joints, connective tissues, viscera, and in 5% of the cases the nervous system. In the CNS juvenile idiopathic arthritis manifests as cerebral vasculitis or cervical myelopathy, in the PNS as compartment syndrome, compression neuropathy, or vasculitic neuropathy (Pineda Marfa 2002).

Rheumatoid arthritis

Though rheumatoid arthritis is predominantly an inflammatory joint disease, there are extra-articular manifestations, including neuropathy (Muramatsu et al., 2008). Neuropathy in rheumatoid arthritis may not only result from entrapment or drug toxicity but also from vasculitis (Agarwal et al., 2008). Rheumatoid arthritis can evolve into rheumatoid vasculitis in 2-15% of the cases and half of these patients may develop vasculitic neuropathy (Schaublin et al., 2005). Vasculitis affects small to medium sized arteries, usually sparing arterioles, capillaries, or venules (Schaublin et al., 2005). Many patients develop a mild sensorimotor, distal PNP or compression neuropathy distinct from vasculitic neuropathy (Schaublin et al., 2005).

Sjögren syndrome

Up to 50% of the patients with Sjögren syndrome develop vasculitic neuropathy (Terrier et al., 2007; Ramos-Casals et al., 2008). Clinically, these patients present with acute onset mononeuritis multiplex or sensorimotor PNP. Histologically, there may be either lymphocytic or necrotizing vasculitis (Terrier et al., 2007). Patients with necrotizing vasculitis appear to have a better response to immunosuppressive therapy than those with lymphocytic vasculitis (Terrier et al., 2007).

Systemic sclerosis (scleroderma)

Scleroderma may be rarely associated with vasculitic neuropathy (Rosenbaum, 2001). Vasculitic neuropathy in these patients manifests as plexopathy (Allanore et al., 2002) or mononeuropathy of a cranial nerve (Allanore et al., 2002). In most patients the autonomic nervous system is additionally
involved (Lagana et al., 1997). Single reports also described patients with mononeuritis multiplex (Nitta and Sobue, 1996).

Waldenström’s macroglobulinemia

Waldenström’s macroglobulinemia is a lymphoplasmodic disorder associated with monoclonal gammopathy (Mauermann et al., 2007). Most commonly patients present with a mild length-dependent sensory neuropathy, which may evolve into multiple mononeuropathies with features of systemic vasculitis (Mauermann et al., 2007) and conversion of type 1 to type 2 cryoglobulinemia. Whether vasculitis in macroglobulinemia is due to the frequent association with cryoglobulinemia or hepatitis C is unknown.

2. Infections disease

Hepatitis associated vasculitis

In a single patient carrying wild-type hepatitis B virus (HBV), vasculitis of the PNS developed one week after influenza vaccination (Wada et al., 2008). Clinically, he presented with mononeuritis multiplex but did not develop involvement of other organs (Wada et al., 2008). Upon sural nerve biopsy predominantly small vessels were affected. The patient made a full recovery under prednisone and lamivudine. A causative role of the vaccination in the development of the vasculitis was assumed (Wada et al., 2008; Takeshita et al., 2006). Vasculitic neuropathy may also be found on nerve biopsy in patients with hepatitis C virus (HCV) infection without cryoglobulinemia (Nemni et al., 2003).

Streptococcus infection-induced vasculitis

An abnormal auto-immune response to beta-hemolytic streptococci A causes vasculitis of the large, medium-sized, or small arteries with deposition of antigen antibody complexes within the vessel wall (Pineda Marfa, 2002). Clinically, affected patients develop Sydenham’s chorea (Pineda Marfa, 2002) or vasculitic neuropathy as the sole manifestation of post-infectious vasculitis (Traverso et al., 1997; Mathew et al., 2007).

Other infections

Rarely, vasculitic neuropathy may be induced by infections with Bartonella henselae (Stockmeyer et al., 2007), or infection with the Epstein-Barr virus (Kanai et al., 2003) or the cytomegalovirus (Schaublin et al., 2005). In single cases vasculitic neuropathy may be even the first sign of an HIV infection (Mahadevan et al., 2001). According to other authors neuropathy has become the most prevalent manifestation of HIV infections (de Freitas, 2007). Vasculitic neuropathy in leprosy is due to affection of the small arterioles either in form of a granulomatous vasculitis or in form of an immune-complex type necrotic vasculitis (Nagasawa, 1999).

3. Sarcoidosis

A number of studies reports on affection of the PNS in sarcoidosis (sarcoid neuropathy, sarcoïd myopathy) (Said and Lacroix, 2005; Vital et al., 2008). Vasculitic neuropathy in sarcoidosis presents as sensorimotor PNP, mononeuritis multiplex, painful mononeuropathies, or as CIDP (Vital et al., 2008). In a retrospective study on 34 patients with sarcoidosis undergoing sural nerve biopsy, 10 (29%) showed vasculitis (Vital et al., 2008). Histologically, vasculitic neuropathy in patients with sarcoidosis is of the necrotizing type (Said and Lacroix, 2005; Vital et al., 2008).

4. Malignancy

Vasculitis is not infrequently associated with malignancies, such as small-cell lung carcinoma, hematologic malignancy (leukemia, myelodysplastic syndrome), lymphoma, renal cell carcinoma, or other solid tumors (Schaublin et al., 2005; Fain et al., 2007). Vasculitis in these patients manifests as fever, cutaneous vasculitis, arthralgias, renal insufficiency, or vasculitic neuropathy in 32% of the cases (Fain et al., 2007). Involvement of the PNS is most frequently seen in patients with solid tumors (Fain et al., 2007). In patients with lymphoma it may be difficult to distinguish if the associated neuropathy is due to lymphoma infiltration or vasculitis (Matsui et al., 2006). Occasionally, anti-neuronal antibodies (anti-Hu, anti-Yo, anti-Ri) are elevated in paraneoplastic, vasculitic neuropathy.

5. Drugs inducing systemic vasculitis

A number of drugs has been reported to induce systemic vasculitis and potentially also vasculitic neuropathy. This is particularly the case with antithyroid drugs, such as propyl-thio-uracil (Frigui et al., 2008). Another, similar drug is benzyl-thio-uracil, which has been reported to induce ANCA positive vasculitis (Frigui et al., 2008). Positive p-ANCA with an MPO pattern has been also reported in another patient treated with benzyl-thio-uracil (Frigui et al., 2008). In a single case the non-steroidal anti-inflammatory drug naproxene induced leukocytoelastic vasculitis of the skin, vasculitic neuropathy, and nephritis (Schapira et al., 2000). Other drugs, reported to cause vasculitic neuropathy include penicillin, allopurinol, cocaine, heroin, valcade, sulphonamides, or phentoin.
Discontinuation of these drugs was beneficial in all these cases (Schapira et al., 2000).

6. Radiation-induced vasculitis

Large vessel vasculitis is a rare complication of local radiation therapy (Rubin et al., 2001). Only in single cases it may affect the vasculature of peripheral nerves. If the axillary artery is predominantly affected, vasculitis may manifest as brachial plexopathy (Rubin et al., 2001).

7. Diabetes

A small proportion of diabetic patients develops proximal neuropathy of the lower limbs, with numbness and pain of the thighs, which worsen during the night. Symptoms progress over weeks and months to disappear spontaneously. In some patients, however, disabling weakness, atrophy, sensory loss, or patellar areflexia may remain (Said and Lacroix 2005). Generally, patients with lumbosacral radiculo-plexo-neuropathies due to vasculitis present with acute or subacute pain and weakness in the lower extremity with unilateral distribution at onset. In 15% of the cases also the cervicobrachial plexus is additionally affected (Schaublin et al., 2005). Contrary to non-systemic vasculitic neuropathy the disease takes a monophasic course with progression lasting weeks or months but slow and incomplete recovery of motor functions (Schaublin et al., 2005).

Non-systemic vasculitis

Vasculitis of exclusively the PNS is not infrequent, although less common than systemic vasculitis (Pagnoux and Guillevin 2005). This condition is also known as non-systemic vasculitis (Pagnoux and Guillevin, 2005). Patients typically present with subacute, painful, multifocal, asymmetric, distal-predominant neuropathy (Collins and Periquet 2004). Patients appear to have a high relapse rate, but low risk of systemic spread, high incidence of chronic pain, relatively good outcome, and low mortality (Collins and Periquet, 2004). After a static period, a slow gradual return of function typically occurs for a given nerve (Schaublin et al., 2005). The outcome is better than with systemic vasculitis and mortality in the majority of the studies low (Collins and Periquet 2004). In a series of 29 patients, however, 37% died after an average of 3.3y after neuropathy onset (Said and Lacroix 2005). In a single patient isolated vasculitis of the sural nerve has been reported (Stickler et al., 2006). Also in a single patient vasculitis neuropathy was associated with elevated anti-cardiolipin antibodies (Jeruc et al., 2006). Clinically, this patient presented with mononeuritis multiplex and had a history of seven spontaneous abortions, Raynaud phenomenon, and livedo reticularis (Jeruc et al., 2006). Sural nerve biopsy revealed necrotizing vasculitis of the epineural arteries with transmural infiltrates and thrombosis (Jeruc et al., 2006). In 6-37% of the cases presumed non-systemic vasculitis actually turns into a systemic vasculitis, which initially exclusively presents with neuropathy (Schaublin et al., 2005, Collins and Periquet 2004, Said and Lacroix 2005). Some authors even doubt that a vasculitis exclusively of the PNS exists and prefer to talk about a systemic low-grade vasculitis, which becomes symptomatic only in the PNS (Said and Lacroix, 2005).

Differential diagnoses

The most frequent differentials of vasculitic neuropathy include axonal polynuropathy of other origin, including borreliosis, Guillain-Barre syndrome (GBS), CIDP, or chronic idiopathic axonal PNP (Vrancken et al., 2004). Rarely, the PNS of patients with T-cell lymphoma may be affected, manifesting as cranial nerve palsies or mononeuritis multiplex (Levin et al., 2008). Affection of the PNS in such patients may be either due to neurolymphomatosis or due to vasculitis (Levin et al., 2008). Infiltration of the PNS by the lymphoma is more frequent than by vasculitis (Levin et al., 2008). Nerve biopsy may help to differentiate between neurolymphomatosis and vasculitis in these patients.

Diagnostic work-up

1. History, examination, blood chemical investigations

History, clinical examination and a routine blood chemical investigation are the basis of the diagnostic work-up for vasculitic neuropathy. Additionally, an electrophoresis, determination of immunoglobulins, complement factors, rheuma factors, anti-nuclear antibodies (ANA), p-ANCA, c-ANCA, MPO-ANCA, and circulating immune-complexes should be carried out. Laboratory tests frequently indicate features of systemic inflammation, such as elevated sedimentation rate, increased C-reactive protein, or positive ANCA (Gorson 2007). ANCA are usually elevated in small vessel vasculitis (Table 1) and necrotizing vasculitis (CSS, Wegener, PAN, Schoenlein Henoch purpura, Kawasaki syndrome), but may be also found in single cases with giant cell arteritis. Pathognomonic for LES are anti-La/SS-BL antibodies...
(Ramos-Casals et al., 2006). Basic essential investigations also comprise a X-ray of the lung to screen for sarcoidosis, eosinophilic infiltration, or lymphoma. If sarcoidosis is suspected a CT of the lung or bronchoscopy is mandatory, as well as the determination of the angiotensin-converting enzyme (Bonfiole and Orefice 2005). VDRL and TPHA should be determined to exclude a luetic infection (Mathew et al., 2007). Determination of antibodies against HBV or HCV are essential to exclude hepatitis-associated vasculitis (Wada et al., 2008). The HIV-status needs to be determined. Cryoglobulins I and II need to be determined from a serum, which has been kept at 37°C to avoid premature precipitation (Schaublin et al., 2005).

2. Electrophysiological investigations

Nerve conduction studies are essential to raise the suspicion of a vasculitic neuropa thy, vasculitic plexopathy, or in selecting the nerve for biopsy (Lacomis and Zivkovic 2007; Sanchez et al., 2001). Not only nerves clinically affected should undergo nerve conduction studies, but also nerves which appear clinically unaffected but may be subclinically involved. Though most frequently motor and sensory fibers are involved, also the autonomic nervous system should be tested. Though the distal portions of motor and sensory fibers are predominantly affected in the majority of the cases, also the proximal parts may be occasionally involved (diabetes), requiring proximal nerve conduction studies. Needle electromyography can be useful to confirm the neurogenic nature of the lesion, particularly in cases with co-pathologies.

3. Nerve biopsy

The golden standard of diagnosing vasculitic PNP is nerve biopsy (Zivkovic et al., 2007). In the vast majority of the cases the sural nerve is biopsied but sensory fibers of the superficial peroneal nerve (N. cutaneous dorsalis) can be also taken (Hilton et al., 2007), although the area of sensory loss may be larger as compared to sural nerve biopsy (Hilton et al., 2007). The sensitivity of nerve biopsy is at most 60% (Oka et al., 2007). It is dependent on the selection of patients, which nerve was selected, timing in relation to symptoms, and the histological criteria applied for diagnosis (Schaublin et al., 2005). A useful target to demonstrate vasculitis on biopsy may be co-expression of the antigens N-epsilon-carboxymethyl-lysine, the receptor for advanced glycation end products (RAGE), or NF-kappaBp65 (Haslbeck et al., 2007). To increase the low sensitivity of nerve biopsy some authors propose to obtain also muscle specimens together with nerve biopsy (Said and Lacroix 2005). The low sensitivity may be also due to the segmental character of nerve vasculitis, why it is proposed to study serial sections of the affected nerve (Said and Lacroix 2005).

Histological findings on nerve biopsy

Histopathologic findings in PNS vasculitis include vasculitis of the large (> 100 mm) nerve arterioles, small (40-100 mm) nerve arterioles (microvasculitis), of capillaries, or the venules (Burns et al., 2007; Vital et al., 2008). Particularly, large or medium nerve arterioles are affected in patients with Wegener’s granulomatosis, PAN, rheumatoid arthritis, or SLE (Vincent et al., 2007; Ohkoshi et al., 1996). Small arterioles are particularly affected in microscopic polyangiitis or mixed cryoglobulinemia (Table 1) (Schaublin et al., 2005). Vasculitis may appear either as lymphocytic/monocytic infiltration or necrotizing degeneration (Terrier et al., 2007). Necrotizing vasculitis occurs in cryoglobulinemia (Tada et al., 2004; Vincent et al., 2007) or Sjögren syndrome (Terrier et al., 2007). Necrotizing vasculitis may be also observed in patients with non-systemic vasculitis and elevated anti-cardiolipin antibodies (Jeruc et al., 2006). Necrotizing vasculitis, predominantly involving the small vessels, and manifesting as mononeuritis multiplex may also develop after influenza vaccination (Wada et al., 2008). Necrotizing vasculitis is also a feature in patients with sarcoidosis (Vital et al., 2008), PAN (Harada et al., 2000; Said 1997), rheumatoid arthritis, SLE, or Wegener’s granulomatosis (Said and Lacroix, 2005). In cases of sarcoidosis and non-systemic vasculitis granulomatous vasculitis can be found (Vital et al., 2008). HBs-antigen can be observed in a high density around the vessels of the epineurium in the sural nerve (Wada et al., 2008). Infiltrates in CSS vasculitis are mainly composed of CD8 positive suppressor and CD4 positive helper T-lymphocytes (Hattori et al., 1999).

Therapy

Treatment decisions should be made in consultation with rheumatologists, infectiologists, hematologists, and oncologists and are dependent on the type of vasculitis, extent and progression of organ involvement, prior responsiveness to any treatment, and presence or absence of a viral infection (Schaublin et al., 2005).

Non-viral vasculitis

For non-viral, systemic vasculitis the application of corticosteroids (1-2 mg/kg/d oral prednisone in mild cases or 1000 mg intravenous methylprednisolone for 5 days followed by daily oral
prednisone during 6-8 weeks in severe cases) is the first line measure (Pagnoux and Guillevin 2005). If corticosteroids are ineffective or if vasculitis relapses upon tapering of steroids, immunosuppression with cyclophosphamide or other immunosuppressive drugs is recommended (Table 4) (Garson, 2007; Djukic et al., 2008). Cyclophosphamide may be applied as intravenous pulses or daily application together with steroids for 3 to 12 months (Garson, 2007; Gorson, 2006). Immunosuppressive therapy can be also applied without additional medication or in addition to corticosteroids, like in CSS associated vasculitis (Zwerina et al., 2008). In patients who do not tolerate cyclophosphamide or have contra-indications, azathioprine, methotrexate, mycophenolate mofetil, or rituximab can be tried (Table 4) (Garson, 2007). Rituximab, administered weekly for 2 weeks in three cases and 4 weeks in six patients, stabilized neuropathy in only one of them. On the contrary, rituximab may be particularly effective in ANCA-positive vasculitis (Eriksson, 2005). Cyclophosphamide can be safely substituted after three or four months by azathioprine or methotrexate without increasing the relapse rate (Schaublin et al., 2005; Gorson, 2006). If steroids and cyclophosphamide are ineffective in CSS, interferon-alpha is an alternative option. Disadvantage of immunosuppression other than cyclophosphamide, however, is that the experience with these agents is limited to single cases or small case series (Garson, 2007; Benamour et al., 2006). No randomized controlled trials have been carried out which assessed the efficacy of a specific treatment (Vrancken et al., 2007).

Additional therapeutic options are immunoadsorption or plasma exchange, which can be effective to eliminate Ro-antibodies but do not seem to improve survival in severe cases (Garson, 2007; Schaublin et al., 2005; Harscher et al., 2007). A further alternative to immunosuppression is the application of immunoglobulins (Garson, 2007). Immunoglobulins may be particularly effective in patients with Sjögren syndrome, SLE, vaccination-induced vasculitis, CSS, PAN, or scleroderma, resistant to immunosuppressive drugs (Levy et al.,

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**Therapy of vasculitic neuropathy (Schaublin et al. 2005)**

**Non-viral vasculitis**

**Steroids**

1-2 mg/kg/d prednisone (mild cases) or 1 g/d methyl-prednisolone iv for 5 d (severe cases) followed by 1-2 mg/kg/d prednisone until effect (6-8 w), afterwards every second day (same dosage or half dosage)

**Cyclophosphamide**

If steroids are ineffective or multi-system involvement either 2 mg/kg during 3-12 m or pulse therapy intravenously with 500 mg/m² once every 4-6 w during 1a

**Methotrexate**

Indicated if cyclophosphamide is ineffective or as long-term therapy after remission under steroids plus cyclophosphamide, start with 0.3 mg/kg (maximally 15 mg) once a week and increase to 15-25 mg/week thereafter

**Azathioprine**

Indicated if cyclophosphamide is ineffective or as long-term therapy after remission under steroids plus cyclophosphamide, at the beginning 1 mg/kg/d later on 2-2.5 mg/kg/d

**Mycophenolate mofetil**

Only pilot studies available, possibly effective in Wegener’s granulomatosis

**Leflunomide**

Only pilot studies available, possibly effective in Wegener’s granulomatosis

**Rituximab**

Only pilot studies available, particularly effective in ANCA-positive vasculitis

**Immunoglobulines**

Open-label studies suggest clinical benefit and reduction of inflammatory markers

**Virus-induced vasculitis**

**Steroids**

Prednisone (1 mg/kg/d) during 1 week followed by a taper during the second week

**Interferon**

IFa-2b or lamivudine during 6m after steroids for hepatitis B-associated vasculitis, in case of hepatitis C, pegylated IFa-2a or IFa-2b, ribaverin (400-600 mg/2x/d) should be added for 1a

**Rituximab**

In pilot open label studies effective in hepatitis C-associated kryoglobulinemia

**Plasma exchange**

May be considered in fulminate cases of cryoglobulinemia
2005). Immunoglobulins are contra-indicated in viral-associated systemic vasculitis (Schaublin et al., 2005).

Virus-induced vasculitis

Therapy in patients with hepatitis B-associated vasculitis should start with steroids during 2 weeks, followed by the application of interferon alpha-2b or lamivudine during 6 months (Schaublin et al., 2005; Wada et al., 2006; Takeshita et al., 2006). In patients with hepatitis C-associated vasculitis therapy starts with pegylated interferon alpha-2a or 2b. Ribaverin can be added during 1 year (Table 4). In patients with vasculitic PNP associated with cryoglobulinemia antiviral therapy with interferon, pegylated interferon, interferon plus ribaverin, or pegylated interferon plus ribaverin may be beneficial in about 80% of the cases (Cacoub et al., 2008; Joshi et al., 2007). Pegylated interferon alpha plus ribaverin are effective in approximately 70% of the cases, but the effectiveness of rituximab is slightly higher (Cacoub et al., 2008).

Prognosis

Approximately 15% of the patients with vasculitic PNP develop malignancy within two years after onset of PNP (Zivkovic et al., 2007). This is particularly the case in patients with Sjögren syndrome or HCV infection, who develop lymphoma more frequently than patients with other causes of vasculitic neuropathy (Ramos-Casals et al., 2006). Despite clinical improvement upon long-term immunotherapy, the overall prognosis of patients with vasculitic neuropathy due to systemic vasculitis remains poor and is often fatal (Schaublin et al., 2005; Fouget, 2000). Though patients with non-systemic vasculitis appear to have a high relapse rate, they have a low risk of systemic spread and low mortality (Collins and Periquet, 2004). The outcome in these patients is better than with systemic vasculitis and better on combination therapy than corticosteroids alone (Collins and Periquet 2004).

Conclusions

Vasculitic neuropathy is an important differential of PNS neuropathy. Vasculitic neuropathy should be considered if there are subacute, axonal, asymmetric sensorimotor, PNP, painful mononeuropathies, including the cranial nerves, pure sensory PNP, or autonomic PNP alone or in association with systemic manifestations of vasculitis, such as headache, cognitive impairment, psychosis, disorientation, hallucinations, stroke, or seizures (CNS involvement) (Harscher et al., 2007), asthma, hemoptysis, alveolar hemorrhage (pulmonary involvement), nephritis, renal failure (renal involvement), hemorrhagic skin lesions, livedo reticularis (skin involvement), or polyarthritis (joint involvement). For diagnosing the condition nerve biopsy is warranted, although in patients with systemic vasculitis and evidence of vasculitis in organs other than the peripheral nerves, nerve biopsy is not indicated. In case of non-viral vasculitic neuropathy therapy should start with steroids and cyclophosphamide. If ineffective, it should be replaced by other immunosuppressive agents. Secondary systemic vasculitis additionally requires treatment of the disorder underlying the vasculitis. The prognosis may be favorable in non-systemic vasculitis but can be fatal in systemic vasculitis.

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