

Case Report

Confocal Cornea Microscopy Detects Involvement of Corneal Nerve Fibers in a Patient with Light-Chain Amyloid Neuropathy Caused by Multiple Myeloma: A Case Report

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Keywords

Confocal cornea microscopy · Small-fiber neuropathy · Multiple myeloma · Skin biopsy · Amyloid neuropathy

Abstract

Changes in the subbasal corneal plexus detected by confocal cornea microscopy (CCM) have been described for various types of neuropathy. An involvement of these nerves within light-chain (AL) amyloid neuropathy (a rare cause of polyneuropathy) has never been shown. Here, we report on a case of a patient suffering from neuropathy caused by AL amyloidosis and underlying multiple myeloma. Small-fiber damage was detected by CCM.

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Amyloidosis is a rare cause of polyneuropathy. There is a distinction between hereditary and acquired forms. A frequent reason for acquired forms is hematologic diseases such as

multiple myeloma, which leads to a generalized deposition of light-chain (AL) amyloid [1]. Amyloidosis often involves the peripheral nervous system, both large and small fibers [2]. It remains particularly challenging to assess small-fiber neuropathy in vivo properly. Beside skin biopsies, confocal cornea microscopy (CCM) is a rapidly developing, noninvasive technique to quantify small-fiber nerves in the subbasal corneal plexus of the cornea. Changes in the subbasal nerve integrity have been described in the late and, more importantly, also in the very early stage of various neuropathies, such as diabetic polyneuropathy, hereditary neuropathies or inflammatory neuropathies [3–6]. Commonly used parameters are the corneal nerve fiber length (CNFL), the corneal nerve fiber density (CNFD) and the corneal nerve branch density (CNBD) [7]. Here, we report on a case of a patient suffering from amyloidosis associated with small-fiber involvement revealed by both skin biopsy and CCM.

Case Presentation

A 79-year-old female Caucasian patient was admitted to our hospital because of a progressive atactic gait disorder. Furthermore the patient complained about paresthesia in all four limbs. A few months before, she had suffered from an acute cardiac insufficiency of unknown origin. An atrial fibrillation and an atrioventricular block II° had been diagnosed and a cardiac pacemaker had been implanted. A few weeks prior to her admission to our hospital, the patient had developed a peripheral facial palsy on the left side, which had initially been interpreted as an idiopathic palsy. A guideline-based treatment with corticosteroids had been started. Except for a former resection of the thyroid gland and a hypertension, there were no diseases in her medical history.

Upon physical examination, we found, apart from the left-sided facial palsy, a symmetric flaccid tetraparesis with distal accentuation. Tendon reflexes were absent. There was a hypoesthesia and paresthesia in the lower legs and paraesthesia in both hands and both lower legs. The Romberg test was positive. The patient was almost unable to remain standing with her eyes closed or even with her eyes open.

Besides a moderate anemia (hemoglobin 6.33 mmol/l) and a hypothyreosis, laboratory tests revealed a monoclonal gammopathy with monoclonal IgG lambda in serum and urine. β 2-microglobulin was elevated. At the same time, diabetes mellitus, hypovitaminosis or rheumatic diseases were ruled out. Cerebral spinal fluid was normal with regard to cell count, protein and lactate. Bone marrow biopsy from the iliac crest revealed a plasma cell neoplasia of 20%. Finally, a multiple myeloma was diagnosed. Skin biopsy (punch biopsy) of the left upper and lower leg showed a total loss of intraepidermal nerve fibers (immunofluorescence staining with anti-PGP 9.5 and anti-Cy3 conjugated IgG). A representative picture of the skin biopsy from our patient is presented below (fig. 1). Electroneurography showed neuropathy with reductions in amplitudes and conduction velocities (table 1). The sensory evoked potentials of the tibial nerve showed a conduction block on the right side and a demyelinating lesion on the left side. Nerve biopsy of the left sural nerve revealed amyloid neuropathy with deposition of AL lambda light-chain amyloid (Congo red stain and anti-AL1, anti-AL7 and anti-lambda light chain), along with a severe reduction of myelinated and unmyelinated nerve fibers.

CCM (Heidelberg Retina Tomograph III with Rostock cornea module, topical medications: GenTeal®, Théa Pharma, Proparacain-POS® 0.5%, Ursapharm, section mode, picture size 384 × 384 pixels or 400 × 400 μ m², used as previously described [8]) was performed by an experienced investigator. Five pictures were taken from the right eye. Picture analysis

was performed with the software ACC-Metrics, Version 2.0 (Xin Chen and Mohammad Dab-bah, Manchester). Average scores were reported: a CNFD of 23.74 nerves/mm², a CNFL of 12.90 mm/mm² and a CNBD of 31.24 branch points/mm². A representative picture of the corneal subbasal plexus from our patient is presented below (fig. 2).

Discussion

Our patient showed a reduction in the CNFL, CNFD and CNBD. With regard to the recently published normative values of corneal nerve parameters, these findings can be interpreted as a severe decrease in the CNFL and a moderate decrease in the CNFD and CNBD [9]. Neuropathy exists in up to 20% of the patients with AL amyloidosis [10]. Apart from the peripheral nervous system, heart, liver, gastrointestinal system and the kidneys are the most affected organs [1]. Hence, it is possible that the cardiac failure of our patient was a symptom of the underlying amyloidosis. Facial palsies as part of an amyloidosis have rarely been described but do occur especially as a bilateral manifestation in hereditary forms [11, 12]. Corneal alterations associated with paraproteinemia or multiple myeloma are well known. Especially keratopathies have been described. Ultrastructural investigations found a corneal deposition of immunoglobulin, which in some cases had fibrils with an appearance similar to amyloid and immunotactoid [13]. However, to our knowledge, a proper deposition of AL amyloid in the cornea has not been reported. There is only one report about changes of corneal nerves in the presence of a multiple myeloma. Parghi et al. [14] report on a patient with a long history of multiple myeloma who finally underwent chemotherapy. Following this treatment, a temporary numbness of the extremities appeared which is typical of chemotherapy-induced polyneuropathy. Other neurological deficits are not mentioned. Corneal assessment (inclusive corneal nerves) was performed with a slit lamp. The authors referred to prominent corneal nerves, which they interpreted as a cause of immunoglobulin deposition. However, this method only permits a crude evaluation of corneal nerves and in that regard cannot be compared to CCM.

To our knowledge this is the first report of an involvement of the subbasal corneal nerve plexus in AL amyloid neuropathy. Corneal small-fiber damage has recently been reported on in various kinds of neuropathy [15, 16]. Basically, small-fiber neuropathy is a common feature of neuropathies caused by amyloidosis. The pathogenesis of this AL amyloid neuropathy is unclear. Obliterations of small arteries, which lead to nerve fiber ischemia, compression of nerve fibers or toxic-metabolic factors, are discussed in the literature [17]. There is a noticeable difference between intraepidermal and corneal nerve fiber reduction in our case. Keeping in mind that the cornea is a bradytroph tissue, artery occlusion as an explanation for corneal nerve fiber alteration seems to be less probable. Therefore, toxic factors as a trigger for changes in the corneal nerves should be considered. In general, it is unknown if the mechanisms of small-nerve fiber damage in the epidermis and the cornea are the same. Ferdousi et al. [7] showed a reduction in corneal plexus parameters in patients with gastrointestinal cancer. Interestingly, all parameters were reduced before chemotherapy was started and improved over the course of time. This suggests small-fiber damage by the tumor, e.g. mediated by an autoimmune process, which also might play a role in the present case.

In summary, our data suggest an involvement of the subbasal corneal plexus, in terms of a small-fiber neuropathy, in a patient with AL amyloid neuropathy. Further studies with

larger numbers of patients in different stages of multiple myeloma with and without associated amyloidosis are needed to confirm our findings.

Statement of Ethics

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Ruhr University Bochum, Bochum, Germany (No. 4905-14).

Disclosure Statement

The authors declare that there are no conflicts of interest to disclose.

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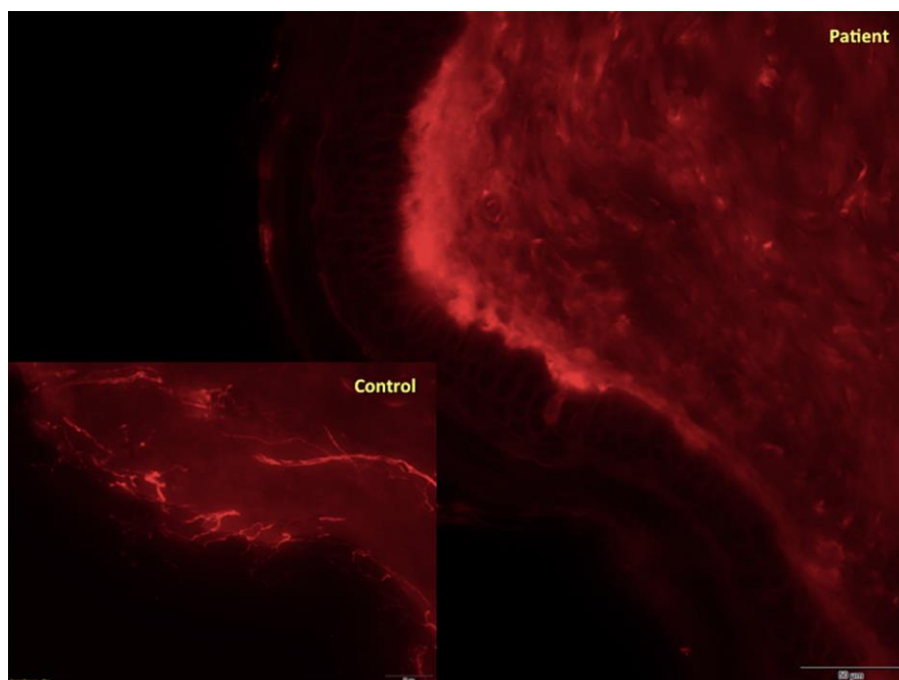


Fig. 1. Representative picture of the skin biopsy (left upper leg). No nerve fibers were detected in the patient's skin biopsy, whereas a control person had a normal nerve fiber distribution (**inset**).

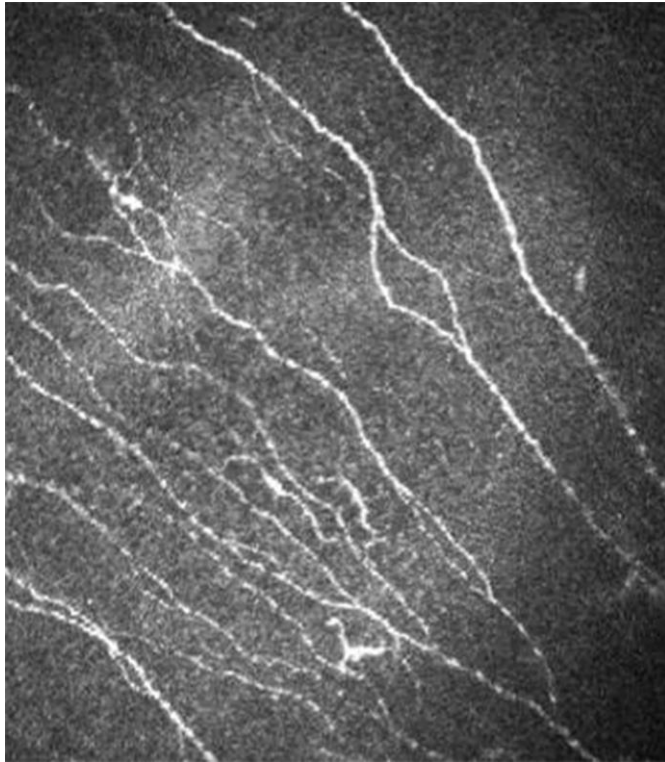


Fig. 2. Representative picture of the CCM.