Pupil abnormality in amyloidosis with autonomic neuropathy

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Abstract

Darkness pupil diameters, light reflexes, and redilatation times have been recorded with infrared TV pupillometry in 12 consecutive patients with systemic amyloidosis associated with sensory motor and autonomic neuropathy. Nine of the patients had AL amyloidosis, two had familial amyloidosis associated with a transthyretin abnormality, and one was untyped. The pupils were abnormal in all 12 patients. On the basis of redilatation lag without pupillotonia, six patients had bilateral Horner’s syndrome and in one of them amyloid deposits were found in a sympathetic ganglion and in the attached sympathetic chain obtained at necropsy. Four patients had bilateral tonic pupils with light-near dissociation and two had abnormally small pupils with reduced light reactions which could not be characterised. It seems that in patients with systemic amyloidosis generalised autonomic neuropathy is strongly associated with pupillary abnormality as shown by tonic reactions with light-near dissociation, by redilatation lag, or by reduced size in darkness.

Keywords: amyloidosis; autonomic neuropathy; tonic pupil; Horner’s syndrome

Clinical involvement of the autonomic nervous system is well recognised, although uncommon, in so-called primary amyloidosis. Among patients who develop polyneuropathy, however, autonomic dysfunction seems to be common. Thus Trotter et al.1 found orthostatic hypotension, bowel upset, and impotence in most such patients. Associated histopathological evidence exists in several case reports of amyloid deposition in sympathetic ganglia and chain.2–4

Ocular involvement is prominent in familial amyloidosis, although rare in primary amyloidosis. Pupillary abnormality has been reported, usually in association with other evidence of dysautonomia. We have found 12 such cases in the literature, the abnormality variously reported as hyporeactive,1 or showing light-near dissociation.7–9 One report describes bilateral Holmes-Adie pupils showing denervation supersensitivity to methacholine.7 These abnormalities are consistent with a defect in the ocular parasympathetic nerves, for which amyloid deposition in the ciliary ganglion may be responsible.6–11

It is surprising that no report exists of Horner’s syndrome, particularly in that the abnormalities associated with autonomic neuropathy in amyloidosis usually include orthostatic hypotension, which may be caused by a sympathetic deficit. In this paper we report findings on 12 patients all having amyloidosis with orthostatic hypotension and pupil abnormality.

Patients and methods

PATIENTS

Twelve consecutive patients (five men, seven women) aged 32 to 70 years with biopsy or amyloidosis established by scan and autonomic failure were studied. In two patients the amyloidosis was familial (transthyretin proline 12 in one, proline 52 in the other), in nine the amyloidosis was biopsy typed as AL and one was untyped. Nine of the patients had peripheral sensorimotor neuropathy. All had orthostatic hypotension with reduced sinus arrhythmia (10 cases), reduced Valsalva response (10), dysphagia (five), diarrhoea (eight), constipation (two), impotence (four) and hypohidrosis (four). Slit lamp examination showed no ocular amyloid deposition except in the two patients with familial amyloidosis who had vitreous amyloid deposits but none in the irides or conjunctivae.

PUPILLOGRAPHY

Pupil diameters and their responses to light and accommodation were recorded without previous dark adaptation by infrared television pupillometry as previously described.12 Sympathetic function of the iris was assessed from measurement of dilator function, which is impaired in Horner’s syndrome causing redilatation lag at the end of the light reflex.13 The index of redilatation time—the t3/4 time—is defined as the time taken for the pupil to recover from its peak constriction during a light reflex three quarters of its way towards the initial darkness diameter.14 The results were compared with normal ranges previously established.14 Drug tests for detection of receptor supersensitivity were not performed because many of the patients had dry eyes.
CASE DESCRIPTION (PATIENT 1)
A previously healthy woman developed a progressive generalised illness from the age of 57 years. She became nauseated and had increasing anorexia, abdominal colic, and diarrhoea, losing 10 kg body weight within 3 months. Subsequently she developed pain and weakness in all limbs with wasting, proximal more than distal, loss of tendon jerks, numbness, and hyperaesthesiae. At 18 months there was orthostatic hypotension and a fixed heart rate with almost no response to deep breathing or a Valsalva manoeuvre. There was proteinuria (1.27 g/24 h), creatinine clearance of 70 ml/min, and a renal biopsy showed AL amyloid deposits. Pupillometry was done at this stage. Renal function deteriorated further, she developed congestive cardiac failure and died 19–20 months after onset of the illness.

HISTOPATHOLOGY
Patient 1 died 6 weeks after the autonomic and pupil examinations. The renal biopsy and necropsy samples were processed for conventional histology and Congo red staining. Immunoperoxidase preparations were made from the paraffin embedded blocks and tested for reactivity for AA amyloid protein and \( \kappa \) and \( \lambda \) light chains by a peroxidase-antiperoxidase technique.

Results

PUPILLOGRAPHY
All twelve patients had abnormal pupils. Except for a small degree of anisocoria in patient 2, only one of his resting darkness diameters lying outside the normal range, all the findings were bilateral. The darkness diameters (right eye only for clarity), the diameters expected on the basis of the patients’ ages, and the principal characteristics of the pupil reflex responses are shown in the table. Patients 2, 5, 6, and 9 had tonic pupils which were irregular in outline; they showed poor reflex responses to light and greater but abnormally slow responses to accommodation (fig 1A).

The resting pupil diameters of patients 3, 4, 7, 8, and 12 were within the normal range;
those of 1 were abnormally small. All light
reflexes were brisk in onset but in each case
there was significant redilatation delay (fig 1B).
The pupils of patients 10 and 11 were
abnormally small and the light reflexes also
small and somewhat slowed. They could not be
characterised reliably.
No relation was found between the profile
of general autonomic dysfunction and the pattern
of pupil abnormality.

HISTOPATHOLOGY
In the kidney from the index case (1), material
with optical staining characteristics of amyloid
was found in the glomeruli, interstitium, and
arterioles (positive Congo red staining with
green birefringence when viewed between
crossed polaroids). Fibrillary amyloid was
demonstrated on electron microscopy. Immuno-
histochemistry showed negative staining for
amyloid A protein and ß light chains but posi-
tive staining for ß light chains. The amyloid is
therefore of the AL type. There was extensive
amyloid deposition in many organs at
necropsy; in particular there was deposition in
the sympathetic ganglia (fig 2).

Discussion
In amyloidosis complicated by autonomic fail-
ure we have found abnormal pupils in 12 out of
12 consecutive patients. This estimate of
prevalence had a lower 95% confidence
interval of 73%, confirming that pupillary
abnormality is indeed common in this situa-
tion. Some of these patients had tonic pupils
with light-near dissociation, indicating para-
sympathetic denervation with reinnervation,
whereas others had redilatation lag without loss
of the light reflex response or tonicity, which is
indicative of sympathetic dysfunction. In one
of the cases with sympathetic dysfunction we
found deposits of amyloid material in a sympa-
thetic ganglion and associated sympathetic
chain. This suggests that some patients have
selective parasym pathetic, others selective sym-
pathetic, damage.

In a condition characterised by progressive
deposition of amyloid material throughout the
peripheral nervous system such disparities
were unexpected. Our findings should, how-
ever, be interpreted with care for minor degrees
doing dysfunction in one branch of the autonomic
nervous system may be undetectable in the
presence of severe damage to the other. Most
particularly, if a pupil is tonic both constrictor
and dilator phases of the light reflex are slowed
and detection of selective redilatation lag
cannot be achieved. We cannot, therefore,
exclude the possibility that most or all of our
patients’ pupils were affected by damage to
both branches of the autonomic nervous
system as would be expected from the
pathophysiology of the condition. On this
basis, it is not surprising that the pupil
abnormality in two of our patients could not be
characterised, nor in the group as a whole that
there was no obvious relation between the pro-
file of the patients’ general autonomic dysfunc-
tion and their particular apparent pupil abnor-
mality.

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