Exudative Age-related Macular Degeneration

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Abstract: In Japan, exudative age-related macular degeneration is defined as a condition in which lesions originating from choroidal neovascularization (CNV) develop in the macular area in association with aging. The symptoms include central scotoma, metamorphopsia, and irreversible and advanced visual impairment. Serous or hemorrhagic retinal pigment epithelial detachment or retinal detachment, subretinal hemorrhage, subretinal connective tissue formation, and scar lesions are noted in the macular area. Fluorescein and indocyanine green can be used as fluorescent dyes for fluorescein angiography, and photocoagulation is performed when choroidal neovascularization outside the fovea is visible on angiograms obtained with either dye. When the CNV involves the fovea, photocoagulation of the entire subfoveal CNV, photocoagulation of the feeder vessel of the neovascularization, interferon β therapy, low-dose radiotherapy, submacular surgery, translocation of the macula, transpapillary thermotherapy, and photodynamic therapy are attempted. Vitreous surgery is performed to remove vitreous hemorrhages originating from the CNV, and procedures for transferring or eliminating subretinal hematomas are performed to treat large subretinal hemorrhages involving the fovea.

Key words: Age-related macular degeneration; Choroidal neovascularization; Diagnostic criterion; Treatment

Synopsis

1. Concept and definition

Age-related macular degeneration can be divided into exudative and non-exudative types. Exudative age-related macular degeneration is a condition characterized by choroidal neovascularization (CNV). It is thought to be a hereditary disease that can be affected by aging and environmental factors and is characterized by hemorrhagic and exudative retinal and retinal pigment epithelial detachment. Atrophic scarring occurs after absorption of the blood and exudates, and severe persistent visual impairment occurs. In Europe and America, exudative age-related macular degeneration is also diagnosed if retinal pigment epithelial detachment is noted, even when no CNV is detected.

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In non-exudative macular degeneration, geographic atrophic lesions consisting of atrophy of the retinal pigment epithelium and the choriocapillaris are noted. While the incidence of this type of macular degeneration is higher than that of the exudative type, progression of the visual impairment is slower.

The prognosis of exudative age-related macular degeneration is particularly poor, and it is predicted that this may soon arise as a serious problem as the number of aged people increases in Japanese society. This type of macular degeneration is therefore discussed below in greater detail.

2. Epidemiology

In 1993, the Research Committee for the Designated Disease Retinochoroidal Degeneration supported by the Ministry of Health, Welfare and Labour conducted a survey jointly with Research Committee for the Epidemiological Study of Intractable Diseases. According to the results of the survey, 14,400 patients with age-related macular degeneration were diagnosed in 1993 in Japan. The overall incidence of age-related macular degeneration is estimated to be 11.5 subjects per 100,000 population (male: 16.2 and female: 7.0), and 7.9, 33.2, 76.1, and 87.2 per 100,000 population in their 50s, 60s, 70s, and 80s (Fig. 1).2)

3. Etiology

Retinal pigment epithelial cells play important roles in maintaining the retinal environment, including regulation of phagocytic activity against the outer segment of the photoreceptor cells, not only in the photoreceptor cell layer, but in the neurosensory retina. Age-related changes in the retinal pigment epithelial cells include accumulation of lipofuscin as the catabolic digestive residue, and lipogenesis. Moreover, Bruch’s membrane beneath the retinal pigment epithelium thickens with aging, and the physiological environment of the photoreceptor cells layer, retinal pigment epithelium, and Bruch’s membrane change.

Neovascularization in the choroid is thought to occur when such excessive age-related changes are combined with an ischemic factor or chronic inflammatory reactions, and ingrowths develop through the damaged Bruch’s membrane and the retinal pigment epithelium and occasionally emerge above the retinal pigment epithelium. An association with heredity3) and smoking4) has also been confirmed.

4. Symptoms

The symptoms include central scotoma, metamorphopsia, and progressive irreversible and advanced visual impairment.

5. Objective findings

(1) Since exudative age-related macular degeneration is characterized by CNV, fluorescein and/or indocyanine green angiography reveals the presence of neovascularization in typical cases. Diagnosis of exudative age-related macular degeneration is performed when CNV is related to aging as indicated by atrophy of the retinal pigment epithelium, pigmentation, and serous drusen. The following findings may also be noted in the presence of CNV:

(2) hemorrhage under the retina or retinal pigment epithelium (Fig. 2),

Fig. 1 Number of patients with exudative age-related macular degeneration under diagnosis (1993)
approach, are currently being assessed. They include photocoagulation of feeder vessels, use of antiangiogenic agents, such as interferon, low-dose radiotherapy, surgical extraction of the CNV region, implantation of the pigment epithelium after extraction of the CNV, and translocation of the fovea.

**Diagnostic Criteria**

1. **Subjective manifestations**
   - Visual impairment
   - Central scotoma
   - Metamorphopsia
   - Micropsia

2. **Objective findings**
   - Findings in the ocular fundus
     1) Subretinal hemorrhage and hemorrhage under the retinal pigment epithelium in the macular area and its vicinity
     2) Serous retinal pigment epithelial detachment
     3) Serous retinal detachment
     4) Disciform lesions (growth of subretinal connective tissue)
     5) Cicatricial lesions
   - Findings on fluorescein fundus angiography

Fig. 1 Hemorrhage under the retinal pigment epithelium (arrow) and subretinal hemorrhage (arrowhead)

Fig. 2 Hemorrhage under the retinal pigment epithelium (arrow) and subretinal hemorrhage (arrowhead)

Fig. 3 Classic CNV involving the fovea detected by fluorescein angiography (left: middle phase of angiography, right: late phase of angiography)
1) Findings on fluorescein angiography

Choroidal neovascularization may be visualized as described below.

(a) Classic CNV (Fig. 3): Hyperfluorescence indicating choroidal neovascularization (CNV) is clearly visualized, and a vascular meshwork structure is seen in the very early phases of fluorescein angiography. In the later phase, marked extravascular leakage can be demonstrated.

(b) Occult CNV (Fig. 4 top): The fluorescein angiographic image of CNV is unclear. Angiographic images obtained in the early phase are ambiguous due to blockage of the CNV by hemorrhage and retinal pigment epithelial detachment. Subretinal pigment epithelial accumulation of dye is noted only in the late phases. Punctate hyperfluorescence is observed in the middle- and late-phases in some eyes.

2) Indocyanine green angiography

There are no established standard views on the interpretation of hyperfluorescence and hypofluorescence on indocyanine green angiograms. However, it is highly likely that occult CNV, which is difficult to detect on fluorescein angiograms because of the presence of hemorrhage or retinal pigment epithelial detachment, is detected by this approach as an area of hyperfluorescence (Fig. 4 middle and bottom). Moreover, since the inflow of dye from the choroidal vessels into the CNV can be observed at an early phase, it is used to detect the vessels feeding the CNV (Fig. 5).

3) Optical coherence tomography

When CNV is present above the retinal pigment epithelium, it is visualized as a bright lesion above the red reflecting layer that represents the retinal pigment epithelium. When the lesion is present beneath the retinal pigment epithelium, differentiation is often difficult.

3. Staging of age-related macular degeneration

(1) Early lesions

1) Serous retinal detachment

Retinal detachment localized to the macular area is noted. A small amount of subretinal hemorrhage, retinal edema (cystoid macular edema),
and hard exudate are occasionally present.

2) Serous and hemorrhagic retinal pigment epithelial detachment

CNV may develop beneath large retinal pigment epithelial detachment, or retinal pigment epithelial detachment may result from choroidal neovascularization. In cases with retinal pigment epithelial detachment and accompanying CNV, a condition in which the margin of the retinal pigment epithelial detachment is depressed, the so-called “notch sign”, is often noted, or the retinal pigment detachment contains a hemorrhage.

(2) Lesions in the exudative stage

Retinal pigment epithelial detachment and serous retinal detachment are induced by large hemorrhages and exudation from the CNV. Retinal detachment (including cystoid macular edema) is often present. The subretinal growth of new vessels and connective tissues is marked, and so-called “disciform lesions” are noted.

(3) Lesions in the scar stage

The CNV regresses, and yellow-white fibrous vascular scar tissue remains under the retina and/or the atrophic retinal pigment epithelium remains. The retinal-choroidal anastomosis and serous detachment may persist. CNV may recur in the area surrounding the scar tissue.

Treatment Approach

The standard approach to the treatment of this condition is photocoagulation. However, it is associated with risks, such as visual impairment induced by the photocoagulation itself, enlargement of the laser scar, and recurrence of CNV after treatment. Therefore, detailed examination by fluorescein angiography is essential.

Moreover, informed consent should be carefully obtained from patients, because the main aim of treatment is prevention of progression, rather than improvement of symptoms. Early detection and early treatment are important, because the lesions enlarge and visual impairment progresses and becomes severe.

1. Photocoagulation

The results of large-sample randomized double-blind clinical studies to clarify the effi-
The efficacy of photocoagulation have been reported in the United States, and they have shown that high intensity photocoagulation after identifying the entire CNV on fluorescence angiograms is effective for extrafoveal, and juxtafoveal CNV, except subfoveal CNV. This approach is also commonly employed in Japan for the treatment of CNV, except subfoveal CNV (Fig. 4, bottom). It promotes scarring of the neovascularization in the exudative stage and absorption of the subretinal fluid and exudate, but it is not indicated in many cases associated with occult CNV, in which the extent of the neovascularization is obscure. Moreover, in eyes with subfoveal CNV, visual impairment is inevitably induced by treatment itself immediately after it is administered. Accordingly, the approaches described below are currently employed in Japan.

2. Photocoagulation of feeding vessels

Photocoagulation of feeder vessels has been attempted for the treatment for subfoveal CNV. Feeder vessels extending from the choroid are identified by indocyanine green angiography, and then selectively coagulated (Fig. 5). Since the area of coagulation is small, the visual impairment induced by treatment is minimized, the fovea is preserved, and improvement of vision can be expected in some patients. Since expertise is required to detect feeder vessels, this procedure is presently being performed at only a few facilities.

3. Administration of interferon β

Regression of small choroidal neovascularization have been reported in the United States, and they have shown that high intensity photoagulation after identifying the entire CNV on fluorescence angiograms is effective for extrafoveal, and juxtafoveal CNV, except subfoveal CNV. This approach is also commonly employed in Japan for the treatment of CNV, except subfoveal CNV (Fig. 4, bottom). It promotes scarring of the neovascularization in the exudative stage and absorption of the subretinal fluid and exudate, but it is not indicated in many cases associated with occult CNV, in which the extent of the neovascularization is obscure. Moreover, in eyes with subfoveal CNV, visual impairment is inevitably induced by treatment itself immediately after it is administered. Accordingly, the approaches described below are currently employed in Japan.

Fig. 6 Clinical course of the patient who underwent extraction of subfoveal CNV
Top left: A preoperative black-and-white photograph. Hemorrhage is noted around the CNV.
Bottom left: A preoperative fluorescein angiogram. Intense leakage suggesting CNV involving the fovea is noted.
Top right: A black-and-white photograph obtained 6 months postoperatively. Part of the sclera is exposed, but the hemorrhage has disappeared. No findings suggesting CNV are observed.
Bottom right: A fluorescein angiogram obtained 6 months postoperatively. No hyperfluorescence suggesting CNV or hypofluorescence suggesting hemorrhage are observed. Hyperfluorescence suggesting scleral tissue staining is noted.
EXUDATIVE AMD

5. Surgical therapy (vitreous surgery, subretinal hematoma transfer procedure, hematoma elimination procedure, and submacular surgery)

When massive subretinal hemorrhage is present, pneumatic displacement or surgical removal of the subretinal hemorrhage is attempted, and vitreous surgery may be indicated in eyes with long-standing vitreous hemorrhage.

Surgical extraction of subfoveal CNV above the retinal pigment epithelium (Figs. 6 and 7) and implantation of the pigment epithelium after extraction have also been attempted. An operative procedure to move the fovea has also been conducted.

6. Photodynamic therapy

In this approach, a photosensitizer is injected intravenously in advance, and after it adheres to the endothelial cells of the CNV, low-power diode laser irradiation is conducted to induce chemical reactions that may cause thrombotic occlusion of the CNV.

Since low-power laser photocoagulation is used in this approach, retinal damage and visual impairment after treatment of the CNV are thought to be minimal. Moreover, treatment can be repeated if the CNV is not obliterated.

A clinical trial of photodynamic therapy is being conducted in Japan and is expected to show promise as a new method for treating subfoveal CNV.

REFERENCES

2) Yuzawa, M., Tamakoshi, A., Kawamura, T. et al.


