Olivopontocerebellar Atrophy with Visual Disturbances

An Ophthalmologic Investigation into Four Generations

PAUL T. V. M. de JONG, MD,* JOOP G. Y. de JONG, MD,† JET M. M. de JONG-TEN DOESCHATE, LLB,‡ J. WILLEM DELLEMAN, MD†

Abstract: Fifty-one members of four generations of a family with autosomal dominant olivopontocerebellar atrophy with decreased visual acuity were examined by an ophthalmologist and a neurologist. Twenty-two persons were affected ophthalmologically and 27 were affected neurologically. We describe the ophthalmologic findings as well as the case history of our youngest patient (age 11 months) from whom we obtained brain tissue and an ophthalmopathologic report at autopsy. [Key words: olivopontocerebellar atrophy, visual disturbance.] Ophthalmology 87:793–804, 1980

Olivopontocerebellar atrophy (OPCA) is a heterogeneous entity that is characterized by the cerebellar phenomena of ataxia and dysmetria with pyramidal, brain-stem, and sometimes extrapyramidal signs. We describe a family with autosomal dominant OPCA with decreased visual acuity which may be classified as type III, according to Königsmark,¹ or as an OPCA variant, according to Eadie.² The purpose of this investigation was to determine the eye abnormalities in the members of this family and to see if any predictive value in relation to later neurologic expression can be attached to particular ophthalmologic symptoms. We also report the case history of, as far as we know, the youngest patient with this condition.

MATERIALS AND METHODS

Fifty-one members of the same family were extensively and independently examined by an ophthalmologist and a neurologist. Their pedigree is shown in Fig 1. After the investigations, the data were collected and compared. Nystagmus and optokinetic nystagmus (OKN) disturbances were taken into account by the neurologist but not by the ophthalmologist. We had so much information on two deceased members of the family that these persons have been included in this report. The following ophthalmologic auxiliary methods of investigation were used: (1) Fundus fluorescein angio-
graphy (FFA) was performed by means of intravenous injection of 3 ml 25% sodium fluorescein, filters Baird Atomic BG12 and Schott GG14 or Spectotech SE 40A and SB 50. (2) The electroretinogram was performed with the aid of two plastic lenses, according to Henkes.3 For the examination of the "photopic" and "scotopic" components of the ERG, we used the method of selective amplification described by Henkes et al.3 The average visual-evoked response (VER) was recorded for each eye separately in all patients; 384 responses were averaged for each eye. In some patients, pattern stimuli as well as flash stimuli were used. In a separate article we will go into greater detail as to the electrophysiologic findings.4 (3) Optokinetic nystagmus (OKN) was registered in the horizontal plane with the method described by Nivilliac.5 The patient was sitting in the center of the drum, speed 54, 90, and 120 degrees/sec, band width 11°. (4) Visual field examinations were performed with the Friedmann Visual Field Analyser and kinetically with the Goldmann or the Tubinger perimeter. In a number of cases, photopic and mesopic static perimetry was used. (5) Dark adaptation was carried out with the Goldmann-Weeke apparatus. (6) Color vision was tested by means of the Farnsworth 100 Hue or 28 Hue test. (7) In a number of cases, the neurologic investigation was extended with a CT brain scan and esophageal roentgen cinematography. We obtained brain tissue at autopsy in four cases, one of which is still being investigated.

RESULTS

Table 1 shows the number of individuals affected ophthalmologically and neurologically and gives the age distribution of all patients. Of the 28 men who were examined, 17 (60.7%) were affected; of the 23 women, 8 (34.7%) were affected. As mentioned before, 5 of the 27 patients had only neurologic disturbances. Table 2 lists the ophthalmologic abnormalities in the 22 patients compared with the 29 ophthalmologically unaffected family members.

Fundus fluorescein angiography was per-
formed on 20 members of the family. The most striking disturbance was a fine, granular pigment dispersion in the macular area, often accompanied by pigment epithelial atrophy and corresponding hyperfluorescence. Fig 2 shows the right eye of patient IX 111 with a time interval of six years. Optic atrophy with narrow vessels was less frequent. Three patients, including
Fig 2. Early FFA of right eye of patient IX 111 at age 27 (top) and age 33 (bottom). The coarse grain throughout the bottom photograph is a technical imperfection.
a 35-year-old, had drusen. Table 3 shows the correlation between the angiograms and the rest of the investigation.

The relationship between the electrophysiological results and the results of the ophthalmologic and neurologic investigation are shown in Table 4.

OKN was registered in six individuals. The nystagmus was either absent or very irregular in all cases, although one of these had neither ophthalmologic nor neurologic symptoms.

Visual field examination was performed on five patients with ophthalmologic symptoms. All showed a relative or absolute central defect corresponding with the visual acuity. We could not find any peripheral restriction or photopic and mesopic discongruencies.

Dark adaptation was tested in only one patient, and was normal.

Color vision tests revealed atypical, acquired defects in seven patients. Table 5 shows the relationship between color vision and ophthalmologic and neurologic disturbances.

The CT brain scan showed excessively wide pericerebellar fluid spaces in five ophthalmologically and neurologically affected patients. In two cases, the perimesencephalic space was excessively large. Fig 3 shows a CT scan with excessive fluid space around the brain-stem of patient X 107 at the age of 30.

Brain autopsy of patient VII 19 (age 87 years) resulted in the following report: pons too small, pons edges narrow, narrow oblongata, excessively large lateral ventricles, excessively wide third ventricle, microscopical cell paucity of the olives, many cells swollen by lipofuscin; very small cerebellum, narrow molecular layer in comparison with a thick granular layer, and the number of Purkinje cells was too small.

A fewer number of Purkinje cells with slight proliferation of Bergmann glia were found in the

| Table 3. Fluorescein Angiography in 20 Members of a Family with OPCA and Visual Disturbances |
|-----------------------------------------------|-----------------------------------------------|
| Normal angiogram                              | 10                                           |
| No ophthalmologic or neurologic signs         | 8                                            |
| Neurologically affected                       | 1                                            |
| Further eye signs                             | 2                                            |
| Abnormal angiogram                            | 10                                           |
| Further eye abnormalities                     | 8                                            |
| Neurologic signs                              | 8                                            |

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<th>Table 4. Correlation between Electrophysiological, Ophthalmologic and Neurologic Findings in 28 Members of an OPCA Family</th>
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+ = affected.
- = non-affected.
R = retina affected.
OC = optic tracts or CNS affected.

N = normal responses.

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<th>Table 5. Relation between Color Vision, Ophthalmologic, and Neurologic Abnormalities in 24 Members of an OPCA Family</th>
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+ = affected.
- = not affected.
cerebellum of patient X 143 (age 11/12 years old) in comparison with a normal child of her age. Fig 4 shows both these cerebella.

In the autopsy report of patient X 11 (age 3 years), no abnormalities were mentioned.

CASE REPORT

The youngest child (patient X 143) was born at term. In the second month of pregnancy, the mother had been exposed to German measles for which she had been given gamma globulin. At the age of three months, the child became tired very quickly, slept a lot, became weaker, and lost contact with her mother. In the fourth month, the mother saw nystagmus for the first time. When 10 months old, the baby still could not turn over from abdomen to back. At that time, the neurologist found psychomotor retardation, hypotonia, low-to-absent reflexes, swallowing disturbances, fine nystagmus, and weak cough and cry. The EEG was somewhat diffusely slowed, echography showed a normal ventricular system, the EMG of the leg muscles as well as the ECG and skull films were normal. The ophthalmologist found normal discs with pallid fundi and finely granular pigmentation in the macular area. The ERG showed almost absent electrical activity. Blood tests and serology were normal; there was no aminoaciduria or increased urinary mucopolysaccharide excretion. At the age of 11 months, she died of aspiration pneumonia and infection.

Laboratory results: hemoglobin 6.8 mmol/liter, slight leukocytosis, erythrocyte sedimentation rate 11 mm, potassium 5.5 mmol/l, SGOT 15, SGPT 9, LDH 14, CPK 0.4, normal renal
functions. Lues serology was negative. Slightly raised IgA, normal IgM and IgG. Lipids: α, β, and pre-β lipoprotein present. Slightly raised triglycerides. Urine analysis: 600 μmol creatinine/24 hours, 21 μmol glucuronic acid/24 hours.

Histopathology revealed a grossly normal retina nasally and in the far temporal periphery. The outer segments (rods and cones) were absent from the optic nerve almost to the equator temporally. The outer nuclear layer was absent just temporal to the fovea, whereas there was a decreased number of nuclei located further temporally. From the equator to the ora, the receptors and their nuclei were of normal appearance. The retinal pigment epithelium (RPE) revealed a few isolated foci of hypertrophy, clumping, and macrophagic activity. Most of the RPE was normal in appearance. The choroid in this celloidin-fixed specimen showed some compression (probably artifact), but no apparent abnormality.

DISCUSSION

In his survey of the literature on the classification of spinocerebellar degenerations, Becker\(^a\) refers to 60 different diseases and syndromes. Refsum and Skre\(^a\) state that there are as many proposed classifications as there are authors on the subject. They emphasize that the classification of inherited ataxias is entirely provisional until it can be related to a specific metabolic disorder, preferably the genetically dependent fundamental biochemical disturbance. That is why we will not go any further into the neurologic subclassification. The neurologist found the following phenomena in this family:

4. Brain-stem functions: Nystagmus, intranuclear ophthalmoplegia, slowing down or absence of OKN, dysarthria.
5. Esophageal, bowel, and bladder function disturbances.

Although the pathologic alterations in the cerebrum of patient VII 19 may partly be attributed to old age, we, nevertheless, thought that we have obtained sufficient support for the OPCA diagnosis. Patient X 143 had too few Purkinje cells in her cerebellum. This may be a result of terminal hypoxia. However, the clinical course and the ophthalmomhistopathologic disturbances, which are in accordance with those described by Ryan,\(^a\) have removed all doubts about the OPCA diagnosis. Patients X 116 and X 117 died at the age of four and one years, respectively, with the same clinical signs as patient X 143. On these grounds and with the CT scan pictures, we concluded that this familial disease is an autosomal-dominant form of OPCA with visual loss, strong penetration, and strongly varying expression. Some parts of the pedigree have not been filled in due to a lack of cooperation. The loss of vision is one of the best indicators that a person is afflicted by the disease, as noted in Table 2. Three members of the family had a severe amblyopia due to convergent squint, one had a decrease of vision as a result of a perforating injury, and one due to a unilateral cataract of unknown origin. Six healthy family members had a minor cataract compatible with their age. Since further ophthalmologic symptoms were absent, these patients have not been described as suffering from OPCA. No decline of vision was found in other healthy members of the family, so that the decline of vision is unlikely to have any predictive value. When the vision decreases, persons are more likely to be affected.

FFA (Table 3), in most cases, did not give any new information. One patient (X 142), with vision 0.5, showed the same slight depigmentation in the macular area (Fig 6) as her cousin, patient X 139, who did not show any other disturbances. In the future, it will have to be shown if this discrete macular hyperfluorescence on the early angiogram has any significance.

It is remarkable that many more affected persons were diagnosed by electrophysiological tests than by the remainder of the neurologic and ophthalmologic tests (Table 4). Of the seven individuals with false-positive results, six had a markedly increased b wave. Here, too, one false-negative result has been encountered. More experience is needed to determine if this is indeed the most sensitive investigation. The same applies to OKN registration.

Color vision (Table 5), visual fields, and dark adaptation tests did not result in any new points of view. In general, it can be said that the findings roughly coincided with visual acuity.

Weiner\(^a\) described a family with OPCA and retinal degeneration in which the youngest patient was 12 years old. He mentioned a 60-year-old man with an advanced macular degeneration with the absence of rods, cones, and ganglion cells in the macular area. Carpenter and Schumacher\(^a\) gave a description of such a family in which three children were afflicted
Fig 4. Cerebellum of patient X 143 (left) and of normal child (right).
of Purkinje cells in the left photograph (hematoxylin and eosin ×360).
Fig 5. A, top, section of macular area of patient X 143 at age 11 months. Note the absence of cones and rods (hematoxylin and eosin ×500). B, bottom, shows normal rods in the periphery (hematoxylin and eosin ×500). Courtesy of A. N. De Haan, MD.
from the age of 11, 14, and 16 months. The clinical picture closely resembled that of patient X 143 mentioned in this report. They did not give any histopathologic report of the cerebrum or eye. In 1971, Ryan\textsuperscript{11} mentioned three patients (a brother, his sister, and her daughter) showing the same signs as our patient. One of these patients showed subnormal ERG and EOG values. In 1975, Ryan\textsuperscript{8} described the ophthalmoscopic findings in two children from the family mentioned by Weiner.\textsuperscript{9} The excessively thin outer nuclear layer with a paucity of cells of patient X 143 is compatible with Ryan's findings in the youngest child, as is the absence of cones and rods in the macula of both eyes. The choriocapillaris appeared to be normal. The loss of the choriocapillaris in elderly patients, as described by Ryan\textsuperscript{11} in 1971, is a rather non-specific picture that is found in several types of macular degeneration. Most of our patients showed, on the fluorescein angiogram, tiny pigment epithelial defects, which gradually became larger (Fig 2), but no primary choriocapillary destruction. In one patient, Ryan\textsuperscript{8} found a normal outer nuclear layer with autolytic receptors, and thought that this might be an indication of a primary affliction of the pigment epithelium. However, our histopathologic examination showed a normal pigment epithelium in the absence of receptors, which would argue for the receptors being initially involved. Early diagnosis is most important for family members, especially when they wish to have children. The FFA might have some predictive value in the teenage group. At this moment, our electrophysiologic findings give so many false-positive results that we cannot speculate on their predictive value until we can re-examine this family in a few years.

ACKNOWLEDGMENTS


REFERENCES

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