Serum levels of retinol-binding protein in different genetic types of retinitis pigmentosa. C. MARAINI, G. FADDA, AND F. GOZZOLI.

The level of retinol-binding protein (RBP) was determined by a single radial immunodiffusion technique in the serum of patients with retinitis pigmentosa (RP) carefully classified according to their specific genetic type, i.e., autosomal recessive, dominant, sex-linked, and other such as those associated with Laurence-Moon-Bardet-Biedl or Winkelman’s disease. Highly purified human normal RBP was used as a standard. In none of the patients with RP studied was the serum level of RBP found to be significantly different from that of the control subjects.

The discovery of a specific carrier protein for vitamin A in plasma has provided a new opportunity for investigating, at a molecular level, the metabolism of retinol in human retinitis pigmentosa (RP). Although no convincing evidence exists of a systemic deficiency of vitamin A in these patients such an investigation was justified by the key role played by this substance for the structural integrity of photoreceptor membranes. The hypothesis that an abnormality in the absorption, transport, or peripheral utilization of vitamin A might be relevant to the pathogenesis of RP receives some indirect support by the degeneration of photoreceptor outer segments produced by feeding young rats with a vitamin A-deficient diet and by the existence of the rare condition of abetalipoproteinemia in which a RP is associated with a defect of vitamin A absorption.

The level of retinol-binding protein (RBP), the main protein responsible for vitamin A transport in plasma, has been determined by Rahi in the blood of patients with RP and found to be on the average 76 per cent of the mean normal adult value; this decreased level of RBP could not be confirmed in another laboratory.

The possibility that a quantitative rather than a qualitative defect of RBP could occur in RP patients, however, existed and a first attempt to answer this question failed to demonstrate any appreciable difference between normal and RP RBP in the ability of this protein to act as a carrier of retinol or interact with prealbumin. These conclusions were confirmed in a further investigation on highly purified samples of RBP obtained by affinity chromatography, thus adding further experimental evidence of a substantial identity between normal and RP RBP.

However, the large volumes of plasma needed for isolation of purified RBP prevent the study of individual patients and require the use of pooled samples from several individuals. For this reason we could investigate qualitatively the characteristics of RBP only in the plasma of patients with the more common recessive type of RP. On the other hand, the existence of multiple genetic types of RP stresses the importance of an accurate classification of these patients in order to exclude that a possible defect is missed in an unclassified sample. We have, therefore, determined the level of RBP in the plasma of individual patients with RP carefully classified according to the specific genetic type, i.e., autosomal dominant, recessive, or sex-linked, as well as several other types such as those associated with Laurence-Moon-Bardet or with Winkelman’s disease. All the patients examined presented a complete clinical and electrophysiologic picture characteristic of the disease.

The sera of 29 normal subjects, randomly distributed in age, were taken as controls. The amount of RBP in serum was estimated by the single radial immunodiffusion technique of Mancini, Carbonara, and Heremans. Sera were stored at -25°C until used. Antiserum agar plates were prepared by mixing Noble agar (2 per cent in barbitone buffer, pH 8.6) with rabbit anti-human RBP serum (final concentration 5 per cent). Sodium azide was added to avoid contamination. Highly purified samples of human RBP obtained from normal plasma by affinity chromatography according to the procedure described by Vahlquist, Nilsson, and Peterson were used as standards.

The results are summarized in Table I. The value of 4.5 ± 1.1 mg per 100 ml of serum found in normal subjects is in very good agreement with those reported from other laboratories. In none of the different genetic types of RP examined in this investigation has the serum level of RBP been appreciably different from that of control subjects. This observation renders it unlikely that a quantitative defect of circulating RBP exists in the more common genetic varieties of RP. However, it should be borne in mind that it

Table I. Levels of retinol-binding protein in the serum of patients with different genetic types of retinitis pigmentosa

<table>
<thead>
<tr>
<th>Genetic Type</th>
<th>RBP (mg/100 ml)</th>
</tr>
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<tbody>
<tr>
<td>Normal subjects (29)</td>
<td>4.51 ± 1.11</td>
</tr>
<tr>
<td>Recessive retinitis pigmentosa</td>
<td>3.5</td>
</tr>
<tr>
<td>Recessive retinitis pigmentosa</td>
<td>4.4</td>
</tr>
<tr>
<td>Recessive retinitis pigmentosa</td>
<td>5.5</td>
</tr>
<tr>
<td>Sex-linked retinitis pigmentosa</td>
<td>5.0</td>
</tr>
<tr>
<td>Dominant retinitis pigmentosa</td>
<td>5.0</td>
</tr>
<tr>
<td>Usher’s syndrome</td>
<td>3.5</td>
</tr>
<tr>
<td>Laurence-Moon-Bardet-Biedl disease</td>
<td>3.5</td>
</tr>
<tr>
<td>Laurence-Moon-Bardet-Biedl disease</td>
<td>5.0</td>
</tr>
<tr>
<td>Winkelman’s disease</td>
<td>3.5</td>
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<tr>
<td>Winkelman’s disease</td>
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</tbody>
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Values for controls are expressed as mean ± standard deviation. Values for retinal degenerations represent single determinations on individual patients.
is possible that some forms of RP might be different diseases even with a common inheritance pattern.12

The probably normal plasmatic transport of retinol in RP does not obviously rule out the possibility that a defect of vitamin A metabolism is at the root of some form of RP. Nothing is known of the intimate mechanism by which retinol is utilized by the pigment and neuroepithelium of the retina. It is clear that only a better knowledge of this basic point at the molecular level in normal and RP eyes will help settle the question whether or not a local disturbance of retinol metabolism is of any importance in this disease.

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REFERENCES

Blood pressure and pressure amaurosis.
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Susceptibility to pressure amaurosis was measured in young research subjects before and during blood pressure elevation induced by intravenous infusions of phenylephrine. Intraocular pressure elevations were produced by paralimbal suction; we measured the highest level to which intraocular pressure could be raised without obliteration of perception of a slowly flickering stimulus in the nasal field of vision. Elevation of systemic blood pressure was accompanied in all subjects by a corresponding increase in the highest "safe" level of intraocular pressure. This observation confirms the commonly held hypothesis that pressure amaurosis is the result of pressure-induced neuroretinal ischemia.

Pressure amaurosis is a sudden loss of vision occurring a few seconds after a marked elevation of intraocular pressure. Depending upon how high the pressure is raised, the amaurosis may be partial or complete. Certain parts of the visual field, including the Bjerrum region, the peripheral area, the nasal field, and the far periphery, lose vision at pressure elevations insufficient to cause amaurosis in the remaining central and temporal portions of the field. Because early loss of vision from glaucoma typically occurs in the same pressure-sensitive areas of the visual field, it is possible that the mechanism for visual loss in pressure amaurosis and glaucoma are similar.

An ischemic mechanism for pressure amaurosis is implied by several observations. First, in order to induce amaurosis, intraocular pressure must be raised to near the diastolic ophthalmic artery pressure. Second, individuals with high ophthalmic artery pressures are, in general, less susceptible to pressure amaurosis than are individuals with low ophthalmic artery pressures. Finally, the blackout of vision in pressure amaurosis resembles that which occurs with postural hypotension or during positive acceleration in aviators, two conditions which transiently lower ophthalmic artery pressure.

These observations do not necessarily exclude the possibility of a nonischemic mechanism. For example, high intraocular pressure might direct-