Congenital Nephropathy Associated with Hearing Loss, Ocular Abnormalities, Mental Retardation, Convulsions and Abnormal E.E.G.

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Probably a new type of congenital nephropathy associated with hearing loss, ocular abnormalities such as cataracts, excessive myopia, strabismus, chorioretinal degeneration, mental retardation, convulsions and abnormal E.E.G., were observed in a 12-year-old male patient.

The patient not only had symptoms resembling familial juvenile nephronophthisis such as polyuria and polydipsia since early childhood, growth retardation, chorioretinal degeneration, anemia and azotemia with few abnormalities of urinalysis, but also showed ocular defects and nerve deafness which have been very often observed in Alport's syndrome. Furthermore, there were mental retardation, convulsions and abnormal E.E.G. which have not been recognized in either of Alport's syndrome and familial juvenile nephronophthisis.

Histological findings of the kidney obtained by open biopsy revealed various changes of the glomeruli such as thickening of mesangium, increased cellularity, hyalinization, and interstitial and periglomerular fibrosis in some parts. These histological findings were entirely different from those of familial juvenile nephronophthisis and somewhat resembled those of “l'hypoplasie rénal bilatérale avec oligoméganéphronie” which was recently described by Royer, Habib and Leclerc.

Recently, hereditary nephropathy has been reported with increasing frequency. However, so far as the diffuse hereditary nephropathies are concerned, the reports have been generally limited to familial juvenile nephronophthisis, Alport's syndrome, and familial hyperprolinemia, etc.

In our previous report, we reported probably a new type of hereditary hematuria associated with mental retardation, abnormal E.E.G., convulsions and ocular abnormalities.

This report is to describe further a case which probably represents a new type of congenital nephropathy associated with hearing loss, ocular abnormalities, mental retardation, convulsions and abnormal E.E.G., which resembled in some respects both Alport's syndrome and familial juvenile nephronophthisis but was entirely different from the both diseases.

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A 12-year-old male. His parents were first cousins and had 4 children, in which the patient was the last one. His father aged 47 years, and two elder sisters (first sister aged 23 years and third sister aged 16 years) had marked short stature without detectable abnormalities of the kidney function, respectively, while his mother and second brother were in a good health. His mother had never suffered from rubella or other diseases during her pregnancy. There was no history of death from renal failure, of deafness, or of ocular abnormalities in his pedigree. He was born on Dec. 6, 1955 at a full term after uneventful pregnancy and delivery, weighing only 1,900 g. After birth, he was frequently attacked by asthmatic bronchitis and sometimes by convulsions. His growth was stunted, and his physical development was so delayed that he could barely sit at the age of 2 years and walk at the age of 3 years.

His parents noticed that the patient had polyuria, polydipsia and slight poor vision since early childhood and slight hearing difficulty late in childhood (at about 8 years of age). His poor vision and hearing difficulty advanced markedly with the progress of age, and growth and mental retardations became marked gradually. Finally, he visited our Clinic on September 21, 1967 for detailed examinations of these abnormalities.

Physical examination on admission revealed that he weighed 22 kg and meas-
ured 114.9 cm (the normal values for a 12-year-old male are 34.6 kg and 141.9 cm, respectively), showing marked stunted growth (Fig. 1). The head showed caput quadratum and the face was markedly anemic. The nose was saddle-shaped and there was horizontal nystagmus. The left eye had apparently noticeable cataract, while the right one was not so manifested. The chest showed barrel-shaped deformity and systolic murmur was heard on the left sternal border in the third interspace. No rales were audible on the both lungs. The abdomen was not so distended, the liver and spleen being not palpable. On the back of the hands, forehead and back of the body there were verrucae planae juveniles. Some ecchymoses were found just under the right eye, and on the upper and lower

TABLE 1. Laboratory results

1. Chemical analyses of the serum:
   - Na (mEq/L) 138–145
   - K (mEq/L) 3.4–6.9
   - Cl (mEq/L) 106–114
   - Ca (mEq/L) 1.9–4.4
   - P (mg/100 ml) 5.5–6.9
   - Blood urea nitrogen (mg/100 ml) 70
   - Venous blood pH 7.20
   - pO₂ (mmHg) 23.5
   - pCO₂ (mmHg) 44.3
   - Bicarbonate (mEq/L) 17
   - Alkaline phosphatase (K.A.U.) 50
   - Uric acid (mg/100 ml) 8.9
   - Total protein (g/100 ml) 6.1
     - Albumin (%) 57.2
     - α₁-Globulin (%) 8.0
     - α₂-Globulin (%) 11.8
     - β-Globulin (%) 11.6
     - γ-Globulin (%) 11.6
   - Cholesterol (mg/100 ml) 192
   - Total lipid (mg/100 ml) 668
   - Phospholipid (mg/100 ml) 242
   - Neutral lipid (mg/100 ml) 84
   - Fatty acid analysis by gaschromatography normal
   - Antistreptolysin-O-titer (U) 50
   - Rubella HAI antibody titer below 8

2. Liver function tests:
   - Bilirubin total (mg/100 ml) 0.3
   - Glutamic pyruvic transaminase (U) 20
   - Glutamic oxaloacetic transaminase (U) 6
   - Lactic dehydrogenase (Wróblewski) 420
   - Zink sulfate turbidity (U) 6
   - Thymol turbidity (U) 2

3. Endocrinological studies:
   - Protein bound iodine (μg/100 ml) 6.9
   - 1³¹ uptake (24 h) (%) 15
   - 1³¹-trisoarb resin sponge uptake (%) 37
   - Urinary 17-KS (mg/24 hr) 2.4
   - Urinary 17-OHCS (mg/24 hr) 0.4
extremities. There was marked edema over the ankles and tibia. The knee reflexes were diminished on both sides.

Laboratory studies. Tuberculin and Wassermann’s reactions were negative. Blood sedimentation rate was slightly accelerated, showing 32 mm per one hour and 74 mm per two hours. Blood pressure was slightly elevated, indicating 136/80 mm Hg. The erythrocyte count was 2,950,000/mm³, hemoglobin 52%, hematocrit 24% and serum iron value 49 γ/100 ml, showing iron deficiency anemia. The thrombotest Owren was 58%, but bleeding and coagulation times, red cell fragility test and thrombocyte count were normal. The leucocyte count was 4,900 per mm³, consisting of neutrophils in 60% non-segmented neutrophils, (10%), lymphocytes in 34%, eosinophils in 3% and monocyte in 3%.

The chemical analyses of the serum, which were repeatedly performed, indicated typical azotemia, showing high levels of blood urea nitrogen (70 mg/100 ml) and phosphorus (5.5–6.9 mg/100 ml), low level of calcium (1.9–4.4 mEq/L) and marked acidosis as shown in Table 1. The alkaline phosphatase (50 K.A.U.) and uric acid (8.9 mg/100 ml) were elevated, probably because of renal osteodystrophy (the former) and uremia (the latter), respectively. Serum creatinine level was 3.7 mg/100 ml. Total protein of the serum was 6.1 g/100 ml, consisting of albumin 57.2%, α₁-globulin 8.0%, α₂-globulin 11.6%, β-globulin 11.6% and γ-

<table>
<thead>
<tr>
<th>Amino acid</th>
<th>Serum (µM/100 ml)</th>
<th>Normal range*</th>
<th>Urine (µM x 10²/24hr)</th>
<th>Normal range†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proline</td>
<td>11.5</td>
<td>11.5–33.0</td>
<td>0</td>
<td></td>
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<tr>
<td>Hydroxyproline</td>
<td>—</td>
<td>0</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Ornithine</td>
<td>—</td>
<td>4.5–9.0</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Arginine</td>
<td>6.9</td>
<td>2.0–14.0</td>
<td>Trace</td>
<td>—</td>
</tr>
<tr>
<td>Methionine</td>
<td>3.4</td>
<td>0.5–4.5</td>
<td>Trace</td>
<td>2.0–9.5</td>
</tr>
<tr>
<td>Aspartic acid</td>
<td>2.5</td>
<td>0.5–1.0</td>
<td>Trace</td>
<td>—</td>
</tr>
<tr>
<td>Valine</td>
<td>16.6</td>
<td>9.0–29.0</td>
<td>6.0</td>
<td>1.5–5.0</td>
</tr>
<tr>
<td>Glutamic acid</td>
<td>9.7</td>
<td>2.5–11.5</td>
<td>9.0</td>
<td></td>
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<tr>
<td>Lysine</td>
<td>16.6</td>
<td>4.0–16.5</td>
<td>18.0</td>
<td>7.0–94.0</td>
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<tr>
<td>Cystine</td>
<td>5.3</td>
<td>1.5–12.5</td>
<td>2.1</td>
<td>4.0–16.0</td>
</tr>
<tr>
<td>Leucine</td>
<td>9.7</td>
<td>7.0–15.5</td>
<td>1.6</td>
<td>2.7–8.3</td>
</tr>
<tr>
<td>Isolecine</td>
<td>5.6</td>
<td>3.5–8.5</td>
<td>4.3</td>
<td>1.8–5.6</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>7.0</td>
<td>3.0–7.0</td>
<td>2.6</td>
<td>2.4–10.6</td>
</tr>
<tr>
<td>Tyrosine</td>
<td>4.7</td>
<td>2.5–6.0</td>
<td>4.1</td>
<td>4.2–16.9</td>
</tr>
<tr>
<td>Threonine</td>
<td>5.5</td>
<td>5.5–17.0</td>
<td>5.4</td>
<td>3.5–24.8</td>
</tr>
<tr>
<td>Alanine</td>
<td>37.8</td>
<td>10.0–40.0</td>
<td>9.0</td>
<td>1.2–44.0</td>
</tr>
<tr>
<td>Histidine</td>
<td>7.4</td>
<td>3.5–9.5</td>
<td>87.0</td>
<td>30.6–128.0</td>
</tr>
</tbody>
</table>

| Glutamine        | —                 | 0.1           | 4.2                    | 30.2–158.7    |

| Serine +         | 40.1              | 19.3–102.5    | 4.2                    | 30.2–158.7    |
| Asparagine       |                   |               | —                      | 6.0–96.9      |
| Taurine          | —                 | 2.5–11.0      | —                      | 16.0–142.0    |
| Glycine          | 35.1              | 4.5–29.0      | 18.7                   | 16.0–142.0    |

* Normal values for the serum are for adults (By Hsia and Inouye, 48 1966).
† Normal values for the urine are for children aged 3–11 years (by Hsia and Inouye, 48 1966).
globulin 11.6%. Antistreptolysin-O-titer was always 50 units. Serum cholesterol, total lipid and the result of fatty acid analysis of the serum by gas chromatography were all normal (Table 1). The liver function tests and the results of endocrine studies were all within normal limits, as shown in Table 1. Chromosomal study revealed a normal karyotype with 46 chromosomes.

First screening tests of the urine for inborn errors of metabolism (ferric chloride test, dinitrophenylhydrazine test, toluidine blue test, ortho-tolidine test, the Nylander and Benedict tests, anilin-oxalate test, Seliwanoff’s test, isatin test and Millon’s test) were all negative. Urinary amino acids were 99 mg per day and the amino acid analysis of the serum and urine by an automatic amino acid analyzer gave normal values, as shown in Table 2.

Rubella HAI antibody titer was below 8, showing that the patient had never suffered from rubella.

The stool was normal in consistency and volume, and showed negative reaction for guaiac test. ¹³¹I-triolein absorption test indicated normal pattern.

The urine volume in 24 hours increased to 1,200–2,200 ml and multiple urinary specimens contained a maximum specific gravity of 1.003–1.006, no or a little protein (0–100 mg/100 ml) and no increase in red and white cells. The urine contained 10 mEq of titratable acidity and 9.4 mEq of ammonium per 24 hours. The culture for microorganisms of the urine gave negative results.

<table>
<thead>
<tr>
<th>Table 3. Renal function tests</th>
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<tr>
<td>P.S.P. test:</td>
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<tr>
<td>(Excretion of the dye in 15 min)</td>
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<tr>
<td>Fishberg concentration test:</td>
</tr>
<tr>
<td>(Maximum concentration capacity, spec. grav.)</td>
</tr>
<tr>
<td>Fishberg dilution test:</td>
</tr>
<tr>
<td>(Maximum dilution capacity, spec. grav.)</td>
</tr>
<tr>
<td>Osmolality clearance test.</td>
</tr>
<tr>
<td>Cosm at concentration</td>
</tr>
<tr>
<td>Creatinine clearance test</td>
</tr>
<tr>
<td>G.F.R.</td>
</tr>
<tr>
<td>R.P.F.</td>
</tr>
<tr>
<td>R.B.F.</td>
</tr>
<tr>
<td>F.F.</td>
</tr>
</tbody>
</table>

Renal function test including P.S.P test, Fishberg concentration test, osmolality clearance test, creatinine clearance test and G.F.R., R.B.F. and R.P.F., etc. were markedly impaired as shown in Table 3. Renogram also revealed marked impairment in the function of both kidneys.

Intravenous pyelogram showed no visualized kidney but a retrograde pyelogram, a normal urinary tract (Fig. 2). A renal arteriogram revealed extremely small kidneys with a very thin cortex without appearance of lucencies suggesting the presence of cyst (Fig. 3).

The roentgenogram of the bones revealed a figure of severe rickets (renal osteodystrophy). Chest roentgenogram and E.C.G. findings indicated left ventric-
cular hypertrophy and the results of cardiac catheterization suggested the presence of aortic valvular stenosis.

Ocular examinations showed horizontal nystagmus, excessive myopia, mature cataract of the left eye (Fig. 4) and incipient cataract of the right eye. (1 year later, cataract of the right eye became mature) (Fig. 5). Electoretinogram revealed no response to stimuli, indicating far advanced visual cell degeneration (Fig. 6).

Audiogram revealed impairment of hearing characterized by a loss in the higher ranges (Fig. 7).

Intelligence quotient of the patient by Suzuki-Binet test was very low, showing the range between 30 and 52. And social maturity scale by Ushijima was also delayed, showing 37 of social quotient.

E.E.G. showed sporadic spikes in the right-occipital and post-temporal areas (Fig. 8).

An open biopsy of the kidney was performed. The kidney was extremely small and microscopically the parenchyma was found to be markedly destroyed. The glomeruli which were thought to be slightly diminished in number and enlarged in diameter (oligomeganéphronie), showed various changes such as
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Fig. 3. Renal arteriogram. Note extremely small kidneys with a very thin cortex. There was no appearance of lucencies suggesting the presence of cyst.

Fig. 4. Left eye of the patient. Note mature cataract.

thickning of mesangium, increased cellularity and hyalinization, etc. (Figs. 9, and 10). Interstitial fibrosis and periglomerular fibrosis were also observed in some parts (Fig. 11). Some tubules were atrophic and some so distended that they formed microcysts. These microscopic findings of the kidney of our own patient were entirely different from those of familial juvenile nephronophthisis, and rather resembled "l'hypoplasie rénale bilatérale avec oligoméganéphromie", which was first presented by Royer, Habib and Leclerc in 1966.40
Fig. 5. Right eye of the patient. Note incipient cataract.

Fig. 6. Electroretinogram of the patient. Note no response to stimuli.

Fig. 7. Audiogram of the patient. Note impairment of hearing characterized by a loss in the higher ranges.
DISCUSSION

As mentioned above, our own patient had not only far advanced renal failure, but also ocular abnormalities such as cataract, myopia, strabismus and chorioretinal degeneration, hearing loss, aortic valvular stenosis, abnormal E.E.G. and mental retardation.

On the other hand, it has been well recognized that the most manifestations of the patient with congenital rubella syndrome are cataract, cardiac anomalies, deafness, low birth weight and mental retardation, and less frequent ones, microcephalus, glaucoma, chorioretinitis, cleft palate and hypospadia, etc.50–57

Namely, our patient had the symptoms similar to congenital rubella syndrome. However, rubella HAI antibody titer of our patient was below 8, showing that he had never suffered from rubella. And further, cataracts and hearing loss of our patient, which had been observed in slight degree since early childhood, markedly advanced with the progress of age, being entirely different from the congenital rubella syndrome.

Because of no history of renal disease, of deafness and of ocular abnormalities in his siblings or pedigree, the condition of our patient should not be called...
‘hereditary’ but ‘congenital’ nephropathy. However, it was of special interest that our patient showed the symptoms resembling in some respects to both familial juvenile nephronophthisis and Alport’s syndrome which have been known to be apparently ‘hereditary’ or ‘familial’.

Familial juvenile nephronophthisis, which was first recognized by Fanconi et al. in 1951, was characterized by familial incidence, anemia and insidious renal failure with polyuria and severe hyposthenuria, but without hematuria, pyuria and proteinuria.

The symptoms have been described in medullary cystic disease of the kidney, which were reported chiefly in the United States and finally was concluded to be the same disease as familial juvenile nephronophthisis.

Some cases of familial juvenile nephronophthisis and of medullary cystic disease of the kidney have been reported to be accompanied by ocular abnormalities such as tapetoretinal degeneration, etc.

The symptoms of our patient resembled in some respects familial juvenile nephronophthisis, showing growth retardation, anemia, polyuria and polydipsia since early childhood, insidious renal insufficiency without hematuria, pyuria and proteinuria, and chorioretinal degeneration, etc. Further, intravenous pyelogram of our patient revealed no visualized kidney, and a retrograde pyelogram showed a normal urinary tract and a renal arteriogram demonstrated extremely small kidneys with a very thin cortex, as usually seen in familial juvenile nephronophthisis. However, in a renal arteriogram of our patient, there was no appearance of lucencies suggesting the presence of cyst, which is characteristic for medullary cystic disease of the kidney. Moreover, our patient showed ocular abnormalities such as cataract, myopia and strabismus, and hearing loss, which have never been recognized in familial juvenile nephronophthisis.

In Alport’s syndrome (familial nephropathy, very often associated with nerve deafness and less frequently with ocular abnormalities), episodic hematuria begins in childhood, and is frequently preceded by an upper respiratory infection and malaise. Progressive evidence of renal insufficiency develops in males and subsequent death in uremia may occur before the thirtieth year of life. The hearing loss, which is characteristically sensorineural with a greater loss in the high tone, and ocular abnormalities such as congenital cataract, congenital nystagmus, congenital myopia, spherophakia, anterior lenticonus, etc, have been known to be associated with this syndrome.

Our patient showed nerve deafness and ocular defects such as cataract, myopia and strabismus which have been considered to be characteristic symptoms of

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Legends for Figs. 9, 10 and 11.

Light microscopic findings of the kidney obtained by open biopsy at the age of 12 years. The glomeruli were slightly diminished in numbers and enlarged in diameter and showed various changes such as thickening of mesangium, increased cellularity and hyalinization, etc. (Figs. 9 and 10). Interstitial fibrosis and periglomerular fibrosis were also observed in some parts (Fig 11).
Alport’s syndrome. However, our patient had no microscopic hematuria, which was the main sign of Alport’s syndrome and showed very similar symptoms to those of familial juvenile nephronophthisis, as mentioned above, which have never been pointed out in Alport’s syndrome.

Furthermore, there were abnormal E.E.G., convulsions and mental retardation in our patient, which have never been pointed out in both Alport’s syndrome and familial juvenile nephronophthisis.

Of course, it was clear that our patient was different from hyperprolinemia, which sometimes showed abnormal E.E.G., convulsions and mental retardation, because of lack of hyperprolinemia.

With respect to histological findings of the kidney, Alport’s syndrome has been described as follows. In the early stage, renal biopsy may show no abnormalities of the glomeruli or tubules, except for blood cell casts in the latter and with the progress of age, changes became typical of chronic glomerulonephritis or pyelonephritis. And in the great majority, foam cells, which were strongly suggestive of hereditary nephritis, were found.

On the other hand, the histologic features of the kidney with familial juvenile nephronophthisis have been known to be interstitial, periglomerular and peritubular fibrosis, hyalinization of many glomeruli and tubular atrophy, dilatation and distortion.

Histological findings of the kidney of our patient showed various changes of the glomeruli such as thickening of mesangium, increased cellularity, hyalinization and interstitial fibrosis and periglomerular fibrosis in some parts. And further, the glomeruli seemed to be slightly diminished in numbers and enlarged in diameter.

These microscopic findings of the kidney of our patient were entirely different from those of familial juvenile nephronophthisis and somewhat resembled "l'hypoplasie rénale bilatérale avec oligoméganéphronie" which was recently described by Royer, Habib and Leclerc. However, ocular defects, hearing loss, abnormal E.E.G. and mental retardation, etc., which were observed in our patient, have not been described in ‘oligomeganepronie.’

The pathogenesis of our case remained unsettled. However, the fact that our patient was a child of consanguineous marriage, suggests that the disease might be caused by some inborn error of metabolism, which is recently being emphasized in the pathogenesis of familial juvenile nephronophthisis of medullary cystic disease and Lowe’s syndrome as well.

Acknowledgment

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