Effects of Renal Transplantation on Hearing and Ocular Changes in a Monozygotic Twin with Alport's Syndrome: Comparison with Other Twin on Hemodialysis

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Aim. To present a unique case of Alport's syndrome in monozygotic twins with two different treatment modalities – renal transplantation and hemodialysis, and to evaluate the effects of therapy on hearing and ophthalmological findings.

Methods. Pure-tone audiogram and ophthalmologic examinations were performed in both twins at the age of 30. At the age of 46, 4 years after renal transplantation in the first twin and after 6 years of hemodialysis in the second twin, both twins underwent control audiometric and ophthalmologic examinations.

Results. Control audiometric measurements showed the progression of bilateral sensorineural hearing loss in the high-frequency range (>2,000 Hz) in both twins. The hearing threshold progressed from initial 50 dB in both twins at the time of the diagnosis to 55 dB in the twin on hemodialysis, and 85 dB in the twin with a transplanted kidney. Retinal blurry hyperpigmentations disappeared in the twin with a transplanted kidney.

Conclusion. In comparison with hemodialysis, renal transplantation in Alport's syndrome may have deleterious effect on hearing, when associated with plasma hyperviscosity and hyperlipidemia, but may lead to regression of retinal hyperpigmentation.

Key words: Alport's syndrome; hearing impairment; hemodialysis; kidney failure, chronic; monozygotic twins; nephritis, hereditary; ocular changes; renal transplantation

Alport's syndrome is one of the most common forms of hereditary nephritis with a typically progressive course and the development of bilateral sensorineural hearing impairment in about 50% of the patients and ocular changes in about 15% of the patients. Abnormalities of platelet number and function (1), leiomyomatosis (2), mental retardation, situ viscerum inversus (3), hyperprolinaemia, hyperprolinuria, and thyroid and parathyroid involvement (4) are only exceptionally associated with the Alport's syndrome. The syndrome is genetically heterogeneous and may be caused by a number of mutations in the COL4A5 gene, which is located on the chromosome X (Xq22). The gene has a significant role in the synthesis of the type IV collagen α5 chain, a fundamental structural component of the glomerular basement membrane, and the basement membrane of the organ of Corti and the lens (5,6). Alport's syndrome incidence has been estimated to 1:5,000 or one-sixth of familial glomerular disease (7). Recent data show that the syndrome is predominantly inherited through the chromosome X (70-80%). In 15% to 20% of the cases, the transmission occurs through autosomal dominant inheritance involving mutations in COL4A3 and COL4A4 genes, whereas it occurs through autosomal recessive inheritance in only 5% of the cases (6-10). As different types of Alport's syndrome vary in the modes of inheritance, they vary in phenotype features as well. The presence and severity of the symptoms are closely related to the age and sex of the patient (11). The course of the disease is different in men and women. Women may act as asymptomatic carriers of the disease, which is manifested by an asymptomatic microhematuria and proteinuria. Clinical course of Alport's syndrome is more severe in affected men. Usually, the progression of the disease is observed in adolescence, but rarely in childhood or be-
between 30-40 years of age, when the syndrome is usually detected as a cause of an end-stage renal disease (12). As the kidney and ear develop between the fifth and the eighth gestation week, the gene mutations occurring at that period may affect both organs, as well as the eye (13).

To our knowledge, there are only two descriptions of Alport’s syndrome in twins: one in a dizygotic (14) and another in monozygotic twins (15). The specificity of our case of monozygotic twins with the Alport’s syndrome is that one of the twin brothers underwent renal transplantation due to renal failure, whereas the other twin remained on regular hemodialysis.

**Case Report**

Diagnostic assessment of an 18-year-old male patient, T.T., who came to us because of severe headaches, revealed arterial hypertension, microscopic hematuria with protein excretion in urine of 0.9 g/day, and increase of the serum creatinine concentration of 140 \( \mu \text{mol/L} \). The patient had no history of severe diseases. The patient’s father had a positive history of renal disease and hearing impairment, and died of uremia at the age of 40. The patient was prescribed antihypertensive medication and advised to have regular checkups with the nephrologist. He refused to undergo a renal biopsy. Two months later, the patient’s brother D.T., a monozygotic twin, was also admitted for identical symptoms. He also had a history of hypertension, microscopic hematuria, and protein excretion in urine of 1 g/day. Serum creatinine concentration was 155 \( \mu \text{mol/L} \). After the possibility of other renal diseases was excluded, the positive family history and nearly identical symptoms supported the diagnosis of Alport’s syndrome in both cases.

Twelve years later, at the age of 30, T.T. underwent renal biopsy due to persistent microscopic hematuria associated with protein excretion, which increased to 2 g/day, and the serum creatinine concentration of 230 \( \mu \text{mol/L} \). Electron microscopy of the biopsy specimen detected thinning, lamelling, reticulation, and fragmentation of the glomerular basement membrane. Light microscopy analysis revealed changes suggesting glomerular sclerosis. Immunofluorescence showed irregular fibrin deposits located next to the glomerular capillary walls.

Sensorineural hearing loss was detected by audiometry in both twins. Hearing impairment was bilateral and mainly affected high frequency ranges (>2,000 Hz), with the hearing threshold of 50 dB in both patients.

Ocular changes were observed only in D.T., who also underwent renal biopsy. Detailed ophthalmologic assessment revealed blurry hyperpigmentation of the retina temporally to the macula of the right eye. The lesion was twice as large as the diameter of the papilla of the optic nerve.

Ten years later, at the age of 40, both twins required regular hemodialysis regime due to the end-stage renal disease. Protein excretion in the urine amounted to >6 g/day, and the serum creatinine concentration was >1,000 \( \mu \text{mol/L} \). Two years later, T.T. received a cadaver renal transplant, and the urea and creatinine serum concentration returned to normal. The patient received immunosuppressive drugs (Prednisone 5 mg/day, cyclosporine A 2.5 mg/kg/day, and azathioprine 1
mg/kg/day). The level of cyclosporine A in his blood was between 100 and 160 ng/mL. Despite hypolipemic drug administration (Simvastatin 20 mg/day), he had hyperlipoproteinemia with serum cholesterol concentration >9.5 mmol/L and triglycerides >5.5 mmol/L. His brother, D.T., remained on hemodialysis regime of 12 hours a week. Four years after the transplantation in T.T., and after 6 years of dialysis in D.T., both twins underwent audiometric and ophthalmologic check-ups and plasma viscosity measurement. In T.T., who received a cadaver renal transplant, pure-tone audiogram above 2,000 Hz in the right ear showed sensorineural hearing loss from 35 dB on 3,000 Hz to 80 dB on 10,000 Hz. In the left ear, pure-tone audiogram above 2,000 Hz showed sensorineural hearing loss from 35 dB on 3,000 Hz to 85 dB on 10,000 Hz (Fig. 1). Ophthalmologic study detected no blurry hyperpigmentation temporally to macula as it was observed 16 years ago. Plasma viscosity determined by capillary viscometry was elevated to 1.71 mPa/s (normal values: 1.43-1.63 mPa/s).

In D.T., who remained on dialysis, pure-tone audiogram above 2,000 Hz in the right ear showed sensorineural hearing loss from 30 dB on 3,000 Hz to 55 dB on 6,000 Hz. There was also a complete hearing loss on 10,000 Hz. Pure-tone audiogram above 3000 Hz in the left ear showed sensorineural hearing loss from 35 dB on 4,000 Hz to 55 dB on 10,000 Hz (Fig. 2). Ophthalmologic examination detected a subtle, net-like blurring of the left lens, spreading bilaterally through the subcapsular posterior plane, as well as through the subcapsular anterior plane. Plasma viscosity determined by capillary viscometry was 1.58 mPa/s.

Discussion

According to Flinter and Chantler (16), three of the four following diagnostic criteria must be present to identify patients with Alport’s syndrome: 1) positive family history of hematuria with or without renal failure; 2) characteristic electron microscopic changes of the glomerular basement membrane on renal biopsy; 3) ocular changes; and 4) bilateral high-frequency perceptive hearing impairment. However, all three diagnostic criteria may not be present at a younger age because ocular changes commonly occur in adult patients (17). About 20% of patients with Alport’s syndrome do not have a positive family history, which suggests that the mutation in COL4A5 gene may develop spontaneously. We did not study gene mutation in our case because the monozygotic twins fulfilled all the criteria for diagnosis of Alport’s syndrome.

Kidney transplantation has proven to be the best method of treatment for the patients with an end-stage renal disease (18). Both our patients had a juvenile type of Alport’s syndrome, including indicators of poor prognosis: male gender, nephrotic syndrome, early appearance of end-stage renal disease, and hearing impairment.

Kidney biopsy was made in an advanced stage of the disease, and characteristic changes of Alport’s syndrome were detected by electron microscopy. The symptoms and clinical course of the disease were almost identical in both patients. Renal transplantation, performed in T.T., led to the improvement of the patient’s condition. The nitric blood substances were back to normal, although an extensive hyperlipidemia persisted due to steroid therapy. D.T. remained on hemodialysis because a matching kidney transplant was not available.

Pure-tone audiogram was performed in both twins at the age of 30, and bilateral sensorineural hearing loss was detected at the high-frequency range, with an average hearing threshold of 55 dB. This type of hearing defect is a typical finding in patients with Alport’s syndrome, and can be observed in other hereditary diseases affecting both the ear and the kidney (19). In patients with Alport’s syndrome and end-stage renal disease, renal transplantation may stop the progression of hearing impairment in most cases (20). Hearing improvement after renal transplantation was described in only one case (19). Mitschke et al (21) have studied hearing prior to and after renal transplantation in patients with the renal failure of varying etiology. Hearing improved in all patients after transplantation except in the few with Alport’s syndrome. Removal of uremic toxins following renal transplantation is most likely the cause of improvement of hearing. The improvement may be due to the lack of electrolyte or osmotic disturbances in the endolymph, which commonly happens after transplantation. In our case, pure-tone audiogram showed more serious bilateral sensorineural hearing impairment at high frequencies in comparison with the findings obtained before the onset of the end-stage renal disease, and with the twin brother on hemodialysis.

The patients received no ototoxic drugs between the first and the last audiometric test. Deterioration of hearing was most likely caused by the interaction between the primary defect of collagen synthesis and plasma hyperviscosity due to hyperlipidemia, provoked by the combined steroid and cyclosporin A therapy that followed renal transplantation (22). It is possible that the increase of plasma viscosity after renal transplantation leads to microcirculation disorders of the inner ear (23). Such an effect of hyperlipidemia has been described by other authors, and usually occurs after a longer period of stability in hearing after renal transplantation (24). Hearing impairment in D.T., who underwent hemodialysis, developed over a longer period of time as a result of the natural course of his fundamental disease as well as electrolytic and osmotic changes in the endolymph, occurring during and after hemodialysis. Additionally, sensorineural hearing impairment could also be related to a secondary nephritic anemia, present in our patient (25).

Blurry hyperpigmentation of the right eye, found in T.T. who later underwent renal transplantation, is a common finding in the patients with Alport’s syndrome (26,27). The other eye had
no retinal spots or anterior lenticous. D.T.’s eyes were free of pathologic changes. Four years after renal transplantation and 16 years after the last ophthalmologic test, no blurry hyperpigmentation of the right eye retina could be observed in T.T.. This finding cannot be interpreted quite easily. The retinal hyperpigmentation is most probably due to the distortion of the retinal pigment epithelium or the epithelium of the Bruch membrane. The possible correlation with the hyperpigmentation of the stria vascularis of the inner ear is also unknown (28). There is no relevant information in the literature regarding possible prospective or retrospective studies on eye changes in the patients with Alport’s syndrome prior to and after renal transplantation. It is possible that subtle subcapsular blurring of the lens (cataract) developed in the twin who remained on hemodialysis as a natural course or a late expression of the disease.

In conclusion, the pathogenesis of hearing impairment and ocular changes in a pair of monozygotic twins with Alport’s syndrome seems to be very complex and does not depend solely on genetic factors but also on a variety of secondary effects of the two different treatment modalities.

References

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