Alport Syndrome: Clinical Update

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Abstract

This review of the literature on Alport syndrome (AS) places emphasis on genetic and clinical issues related to the sensorineural hearing loss in type III and type IV X-linked AS. The review covers prevalence, medical issues, genetic issues, audiologic findings, vestibular findings, the pathophysiology of hearing loss in type III AS, age- and phenotype-specific normative data and concludes with a discussion regarding future auditory-genetic research with AS.

Key Words: Alport syndrome, genetic heterogeneity, linkage-analysis, phenotypic heterogeneity, X-linked

In 1927, Alport described a kindred with dominantly inherited kidney disease that was characterized in both sexes by red blood cells in the urine (hematuria), red blood-cell casts in the urine, variable amounts of protein in the urine (proteinuria), and a predilection in males for progressive "perceptive deafness." The hematuria was a chronic sign, present at birth and showing exacerbation with upper respiratory and other infections. Affected males died during adolescence from renal failure (end-stage renal disease, ESRD), and, due to their poor health, they produced no offspring.

Today, Alport syndrome (AS) is conceptualized as a group of hereditary diseases characterized by progressive defects of capillaries in the glomerular basement membranes of the kidneys (glomerulonephritis), with various nonrenal features including progressive sensorineural hearing loss (SNHL), ocular problems, and blood platelet defects (Savage et al., 1986; Rumpelt, 1987; Atkin et al., 1988b). According to Atkin et al. (1988b), AS may have seven subtypes (Table 1), which exhibit juvenile and adult forms and two modes of inheritance.

PREVALENCE OF AS

AS has been reported throughout the world, it is not associated with any race or geography, and the worldwide prevalence of AS has not been determined (Atkin et al., 1988b). The incidence of AS has been reported at 1 in 200,000 (Brown et al., 1986). According to Fraser (1976) and Konigsmark and Gorlin (1976), AS accounts for approximately 1 percent of genetic hearing loss. Table 2 displays a breakdown in percentages of AS individuals receiving dialysis and kidney transplant versus those developing ESRD for Europe, the United States, and Utah (Brunner et al., 1978; Gottschalk et al., 1978; Atkin et al., 1988b).

MEDICAL ISSUES

Differential Diagnosis

AS has traditionally been difficult to define clinically. Currently, there is no universally standardized method for differential diagnosis. Atkin et al. (1988b) point out that over 40 conditions have been reported as hereditary nephritides. In addition, Gubler et al. (1981) caution that: "Renal disease with hearing loss, even if familial, should not be equated with Alport syndrome.... Truly congenital hearing loss is unlikely to be due to Alport syndrome" (p. 493). Consequently, proper differential diagnosis for AS should rule out all other causes of hematuria. A diagnostic work-up to provide refined
Table 1 Classification of Alport Syndrome

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
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<tbody>
<tr>
<td>I</td>
<td>Autosomal-dominant mode of inheritance, juvenile onset for ESRD and SNHL</td>
</tr>
<tr>
<td>II</td>
<td>X-linked dominant mode of inheritance, juvenile onset for ESRD and SNHL</td>
</tr>
<tr>
<td>III</td>
<td>X-linked dominant mode of inheritance, adult onset for ESRD and SNHL</td>
</tr>
<tr>
<td>IV</td>
<td>X-linked dominant mode of inheritance, adult onset for ESRD and normal hearing</td>
</tr>
<tr>
<td>V</td>
<td>Autosomal-dominant nephritis, SNHL, and thrombocytopenia (blood platelet defect)</td>
</tr>
<tr>
<td>VI</td>
<td>Autosomal-dominant juvenile nephritis and SNHL</td>
</tr>
</tbody>
</table>

Adapted from Atkin et al., 1988a.

phenotype characterization for genetic linkage analysis should include a combination of medical examination, accurate and complete family history, careful urinalysis, and audiologic assessment (Gregory et al., 1990, 1991).

Early identification of AS is important to prevent and counter the effects of associated high blood pressure and kidney dysfunction. Equally important, a correct diagnosis is essential to avoid using an unidentified, gene-carrying family member as a kidney donor.

Medical Management

Optimal medical care for AS includes controlling blood pressure, avoiding ototoxic drugs, a low-protein diet, monitoring visual acuity, and an eventual kidney transplant or dialysis treatment (Atkin et al., 1988b). Genetic counseling and audiologic management are also helpful.

Medical Prognosis

Once diagnosed, the prognosis for a person with AS is variable. Prognosis depends upon the disease subtype and the age of diagnosis (Atkin et al., 1988b).

Table 2 Prevalence of Alport Syndrome for Persons Needing Dialysis/Kidney Transplant or Having End Stage Renal Disease

<table>
<thead>
<tr>
<th>Europe (%)</th>
<th>USA (%)</th>
<th>Utah (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dialysis/K. Transplant</td>
<td>3.0</td>
<td>2.2</td>
</tr>
<tr>
<td>ESRD</td>
<td>1.0</td>
<td>-</td>
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- = no data.

GENETIC ISSUES

AS is phenotypically, and perhaps genetically, heterogeneous X-linked dominant nephritis that results from different mutations of the COL4A5 collagen gene (Barker et al., 1990). More than one gene or gene mutation produces the disease (genetic heterogeneity), and AS can show tremendous clinical variability between kindreds (phenotypic heterogeneity) (Gregory et al., 1990).

In adult X-linked AS, the hearing loss for the standard test frequencies (STFs) is different in progression, degree, and audiometric contour from descriptions of hearing loss reported with juvenile AS. The adult audiologic data confirm phenotypic heterogeneity and support a theory of auditory genetic heterogeneity in AS (Barker et al., 1990; Gregory et al., 1990; Zhou et al., 1991).

Recent genetic linkage studies using restriction fragment length polymorphisms (RFLPs) technology and clinical tests of renal function to define the phenotype have mapped type III AS to near Xq22, with little evidence for genetic heterogeneity (Atkin et al., 1988a; Gregory et al., 1990). It is noteworthy that the two adult-type AS kindreds from the Utah studies had single base mutations; however, to date, there appear to be no clear connections between the severity of SNHL or severity of renal disease and the site or position of mutants in COL4A5 (Gregory, 1991). Thus, both renal and auditory genetic heterogeneity in AS are hypothesized but need molecular level confirmation.

Recently, new DNA probe markers became available, which effectively reduce the number of affected family members required for a successful linkage analysis with adult X-linked AS (Barker, personal communication, 1992). Linkage analysis studies of AS using an auditory classification of phenotype should be initiated. Finally, Kimberling (1991) mentioned that AS represents the first hereditary hearing loss condition in which the gene has been identified and cloned to study its biochemical nature at a molecular level.

AUDIOLOGIC FINDINGS IN AS

Approximately 45 percent of AS females and 55 percent of males are reported to experience a slowly progressive, symmetrical, mild to moderately severe, mid- and high-frequency SNHL (Sohar, 1956; Cassidy et al,
Auditory Phenotypes in AS/Wester


Rintelmann (1976) reported wide variability in the degree of hearing loss and audiometric contour. Males generally show more severe hearing loss. Females typically show only a mild degree of hearing loss (Wester, 1990). Only Zollinger and Mihatsch (1978) mentioned an asymmetric SNHL following the renal disorder in AS. Bergstrom et al (1979) reported a mixed hearing loss as typical in AS; however, that observation has not been confirmed in subsequent studies.

Hearing loss has recently been reported as one of the first symptoms of AS (Gleeson, 1984; Flinter et al, 1988; Wester, 1990); it can occur as early as 10 years and has been described as socially nonsignificant until the second decade of life (Gubler et al, 1981; Gleeson, 1984). Wester (1990) documented the simultaneous deterioration of STF and ultra high-frequency (UHF) hearing in adult type III AS and conjectured involvement of the entire stria vascularis rather than progressive involvement from the basal to the apical end of the cochlear partition. Arnold (1983) indicated that the SNHL generally followed progressive renal dysfunction. Eichwald (1978) obtained statistically significant and moderate correlations between the degree of hearing loss and renal dysfunction on adult type III AS persons. He used the pure-tone average, blood urea nitrogen, and blood creatinine, respectively, as covariates.

PATHOPHYSIOLOGY OF HEARING LOSS IN AS

Temporal Bone Findings

A clear understanding of the cellular-level cochlear changes in AS have been clouded by the inherent difficulty of histopathologic analysis (Arnold, 1983). Early reports included loss of basal spiral ganglion cells, degeneration of the stria vascularis and hair cells of the organ of Corti, as well as reports of no clear association of damaged cochlear tissues, (Gregg and Becker, 1963; Babai and Bettez, 1968; Fujita and Hayden, 1969; Westergaard et al, 1972; Bergstrom et al, 1972).

Arnold (1983) reported electron microscope studies of two temporal bones that were appropriately processed. He found that the most severely involved cochlear structure was the stria vascularis, which showed thickening and lamination similar to that of the capillary basement membrane in the classic glomerular lesion. In contrast to the typical renal lesion, there was no evidence of intramembranous granules (Arnold, 1983). Near the origin of Reissner's membrane, Arnold found extensive marginal cell loss and perivascular intercellular edema. The remaining strial epithelial cells were characterized by vacuolation and apical cytoplasmic protrusions.

Johnsson and Arenberg (1981) studied four AS cases and found severe atrophy of the stria vascularis in the middle and apical turns. Abnormalities and degeneration of the stria vascularis have been correlated with the SNHL in AS (Pauler et al, 1988).

Etiologic Issues

Controversy exists regarding the etiology of SNHL in AS. This is focused upon a direct genetic effect versus a secondary environmental/metabolic or iatrogenic effect. Johnsson and Arenberg (1981) and Arnold (1983) have proposed that the SNHL in AS may represent a secondary metabolic effect of the progressive kidney dysfunction. They further suggested that ototoxic medications used in the medical management of kidney patients undergoing transplants were an additional explanation for the associated SNHL. The findings of McDonald et al (1978) also support the indirect

VESTIBULAR FINDINGS IN AS

Very few systematic oculovestibular function assessments have been reported with AS. Histologic sections have shown cyst-like vesicle formations under each utricular macule, which could support a cellular level basis for disequilibrium in AS (Celsius-Blaubach et al, 1974; Oda et al, 1974). Nystagmus was not consistently confirmed as an ocular symptom in AS by Perrin (1964). Caloric testing has been equivocal with reports of normal and bilaterally decreased caloric response (Suzuki and Kan-
From a genetic perspective, Wester (1990) found that the progressive SNHL of adult types III and IV AS was consistent with the X-linked mode of inheritance established by mutation analysis in two kindreds studied by Barker et al (1990). Thus, the SNHL in adult X-linked AS may represent allelic variation, rather than a separate genetic or indirect uremia-related condition. Additionally, confirmation of hearing loss years to decades before the findings of elevated serum creatinine levels (the first indication of kidney dysfunction) supported a direct genetic effect (Wester, 1990). Finally, the documentation of hearing loss in subjects with otherwise unremarkable auditory histories suggested a direct genetic effect (Wester, 1990).
Figures 1, 2, 3, and 4 are mean composite STF and UHF audiograms that illustrate the deterioration of hearing sensitivity as a function of age and gender for types III and IV AS (Wester, 1990). The individual audiologic characteristics typically included a flat to gently sloping, mild to moderately severe sensorineural hearing loss, with preserved word identification (90% to 100%) and a manageable dynamic range of 30 to 60 dB HL. AS patients typically did very well with amplification.

**DISCUSSION**

Wester (1990) described the progressive hearing loss by age and gender for type III AS but only partially completed age and gen-
under norms for type IV AS. No clear pattern of UHF hearing loss developing prior to involvement of the STFs emerged from that data as hypothesized in young adult type III AS males (ages 21 to 30 years), hearing loss first appeared at all STFs and UHFs. This finding differed from the earlier reports that described severe high-frequency hearing loss in the STFs (Sohar, 1956; Rintelmann, 1978; Gleeson, 1984; Flinter et al, 1988). This difference may have reflected previous studies of juvenile forms of AS. Although they provided no description of their kindreds in terms of adult versus juvenile nephritis, it is the documentation of hearing loss in children alone that suggests that those kindreds had juvenile types I, II, or VI AS.

Thus, one priority for future research is the continued collection of hearing sensitivity data for type IV AS. Continued documentation of SNHL in men and women with type IV AS and otherwise unremarkable auditory histories will have implications to include late-onset mild SNHL as a characteristic of type IV AS in Atkin's classification scheme. To that end, UHF audiometry is recommended along with STF testing, family history, and other clinical tests.

Konigsmark and Gorlin (1976) point out that contrary to popular thought, many hereditary hearing losses are asymmetrical in audiometric contour. In adult X-linked AS, however, the progressive SNHL is remarkably symmetrical for audiometric contour across age and gender (Wester, 1990). Audiologic confirmation of either unilateral or asymmetrical hearing loss in adult X-linked AS subjects would most likely signify an additional systemic or environmental etiology. Thus, for either clinical or linkage analysis of AS, an in-depth auditory history is critical for the rigorous exclusion of extraneous causes of SNHL.

The use of audiologic procedures for genetic linkage research should be evaluated from three perspectives. The first is the efficacy for early (even subclinical) identification. Second, all audiologic procedures, whether behavioral or electrophysiologic, are at best an indirect reflection of a biochemical gene action. Thus, any audiologic procedure used to clinically define the phenotype for linkage analysis should be as "close" to gene action as possible. Auditory functions measured by behavioral audiometry represent complex levels of phenotype description "distant" from gene action. As such, behavioral testing is subject to greater modification by multiple genetic and environmental factors (Fain et al, 1986), which may lead to marked variability in the phenotype classification. Consequently, the use of behavioral tests should be minimized in the context of genetic linkage studies. Finally, the audiologic procedure(s) should provide information to improve the overall understanding of auditory physiology for any particular condition.

In Wester's (1990) study, behavioral audiometry enhanced the clinical description of phenotypes between type III and IV AS; however, behavioral audiometry did not help with early identification to rule out suspected gene carriers. Behavioral audiometry should be limited to normative age and gender-referenced hearing sensitivity studies with other AS subtypes.

In summary, electrophysiologic procedures should provide more germane specification of auditory phenotype(s) for correlation with molecular genetics. Future linkage analysis with AS should include the use of otoacoustic emissions and electrocochleography to provide more direct cellular-level data for phenotype classification (Fain et al, 1986). Such objective data will also provide improved information on the neurophysiologic nature of SNHL in AS.

Whether objective procedures will contribute to early identification of individuals at risk for AS needs to be systematically determined. Linkage analysis correlated to objective audiologic procedures may provide confirmation of hypothesized auditory genetic heterogeneity in AS.

REFERENCES


Auditory Phenotypes in AS/Wester