Genetic Study of Syndromic Inherited Deafness
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Abstract
The study comprised 25 patients with Syndromic genetic hearing loss. They were selected from the Audiology Unit, Faculty of Medicine, and the Human Genetics clinic, Medical Research Institute, Alexandria University. Their ages ranged from 2.5 to 19 years. Males were more affected than females (M/F ratio = 2:1). The high parental consanguinity (63.2 %) emphasizes the contribution of autosomal recessive gene or multiple genes in the etiology of deafness.

Thorough clinical examination, and complete investigation including metabolic screening tests, cytogenetic studies and other specific investigations, together with pedigree analysis were the main criteria for diagnosis. Fundus examination was essential as ocular involvement was found in association with most cases of genetic hearing loss. Results of the studied patients revealed that deafness was inherited either dominantly, recessively or in X-linked manner in association with other anomalies in the following syndromes: Down syndrome (one case, 4%), external ear malformation (4%), distal arthrogryposis (one case, 4%), Optic atrophy and ataxia (one case, 4%), Stickler-Wagner syndrome (one case, 4%), Usher syndrome (2 cases, 8%), Waardenburg syndrome types I and II (2 cases, 8%), Charcot-Marie-Tooth syndrome (2 cases, 8%), Alport syndrome (3 cases, 12%), Pendred syndrome (5 cases, 20%), and Hunter syndrome (3 cases, 12%). For the idiopathic cases (2 cases, 8%), a possible genetic cause was also suggested, probably autosomal recessive.

Introduction
Deafness is a feature among a group of clinically recognizable signs that together comprise a syndrome. Inherited Syndromic deafness constitutes about 40% of all genetically determined deafness. Hearing loss is a major component of more than 100 syndromes, the majority of which are rare. Syndromic hearing loss is quite heterogeneous at both the phenotypic and molecular levels. The most common syndromes are Usher syndrome, Pendred syndrome, Waardenburg syndrome and Alport syndrome. (1)

As hereditary deafness is associated with multiple organ systems anomalies, so their classification is arbitrary, based upon the body system whichever is predominantly involved. (2)

Occasionally, deafness is found in association with well-established syndromes in which it is not usually a component; or in association with structural abnormalities which do not constitute a known syndrome. This type of deafness is non-familial, and is classified as cryptogenic or idiopathic deafness. Genetic causes are highly suggested to be the cause of deafness in this type. (2,3)

The present work was aimed to study the genetic profile of different syndromes associated with deafness and their mode of inheritance, also to determine the possible genetic cause in idiopathic deafness, in order to obtain a precise diagnosis which is critical for the effective management and for appropriate genetic counseling.

Subjects and Methods
This study comprised 25 patients with Syndromic deafness. They were chosen from the Audiology unit, Faculty of Medicine, and the Human Genetics clinic, Medical Research Institute, Alexandria University. Their ages ranged from 2.5 to 19 years. Patients with past history of exposure to infections or teratogenic
agents either during prenatal perinatal or postnatal periods were excluded.

Provisional diagnosis was made according to genetic history, pedigree analysis, and full detailed physical examination to identify abnormalities in other systems, which would permit the establishment of a syndromic diagnosis. Ophthalmologic assessment was done in indicated cases. Anthropometric measurements (4,5) and audiometric evaluation (6,7) were done to all patients. Other investigations were done in indicated cases, as CT scan of the brain, X-ray and ultrasonography. Metabolic screening tests including thin layer chromatography and urine analysis for proteinuria were done in indicated cases. Cytogenetic studies were performed for suspected chromosomal anomalies by G-banding technique (8).

Table I: Distribution of studied patients according to their diagnosis and mode of inheritance.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Nº. of cases</th>
<th>Sex ratio (M:F)</th>
<th>Consanguinity ratio</th>
<th>HL</th>
<th>Mode of inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromosomal syndrome (down syndrome).</td>
<td>1</td>
<td>1:0</td>
<td>0:1</td>
<td>SN</td>
<td>AD</td>
</tr>
<tr>
<td>Microtia, mental atresia and deafness.</td>
<td>1</td>
<td>0:1</td>
<td>0:1</td>
<td>CD</td>
<td>Polygenic</td>
</tr>
<tr>
<td>Distal arthrogryposis and deafness.</td>
<td>1</td>
<td>0:1</td>
<td>1:0</td>
<td>SN</td>
<td>AD</td>
</tr>
<tr>
<td>Progressive optic atrophy, ataxia and deafness.</td>
<td>1</td>
<td>1:0</td>
<td>1:0</td>
<td>SN</td>
<td>AD</td>
</tr>
<tr>
<td>Stricter – Wagner syndrome.</td>
<td>1</td>
<td>1:0</td>
<td>1:0</td>
<td>SN</td>
<td>AD</td>
</tr>
<tr>
<td>Usher syndrome.</td>
<td>2</td>
<td>0:2</td>
<td>2:0</td>
<td>SN</td>
<td>AR</td>
</tr>
<tr>
<td>Waardenburg syndrome (type 1,11).</td>
<td>2</td>
<td>1:1</td>
<td>0:2</td>
<td>SN</td>
<td>AD</td>
</tr>
<tr>
<td>Charcot – Marie – Tooth disease, and deafness.</td>
<td>2</td>
<td>1:1</td>
<td>2:0</td>
<td>SN</td>
<td>AR</td>
</tr>
<tr>
<td>Alport syndrome.</td>
<td>3</td>
<td>3:0</td>
<td>3:0</td>
<td>SN</td>
<td>AD/XL</td>
</tr>
<tr>
<td>Pendred syndrome.</td>
<td>5</td>
<td>3:2</td>
<td>5:0</td>
<td>MX</td>
<td>AR</td>
</tr>
<tr>
<td>Hunter syndrome.</td>
<td>3</td>
<td>3:0</td>
<td>1:2</td>
<td>SN</td>
<td>XL</td>
</tr>
<tr>
<td>Indefinite diagnosis.</td>
<td>1</td>
<td>1:0</td>
<td>1:0</td>
<td>SN</td>
<td></td>
</tr>
<tr>
<td>Idiopathic deafness.</td>
<td>2</td>
<td>1:1</td>
<td>1:1</td>
<td>SN</td>
<td></td>
</tr>
<tr>
<td>Total.</td>
<td>25</td>
<td>2:1</td>
<td>3:1</td>
<td>app</td>
<td></td>
</tr>
</tbody>
</table>

Results and Discussion

All cases are probably hereditary as they were selected without any acquired cause of deafness. The study comprised 25 patients, 16 males and 9 females. They were included in 19 families. Table I shows the distribution of cases according to their diagnosis, consanguinity ration, sex ratio, type of hearing loss and mode of inheritance. The study revealed that 22 patients have known diagnosis of hereditary syndromic deafness, one patient had indefinite diagnosis and two patients had idiopathic deafness. The excess of affected males than affected females (M/F ratio = 2 : 1) could be attributed to genetic causes (9).

Parental consanguinity was found in twelve families (63.2%), ten of which were first cousins (52.6%). This high rate of consanguinity was significantly higher (p < 0.05) than the consanguinity rate (28.9%) in the Egyptian population (10). This emphasizes the contribution of autosomal recessive gene or multiple genes in the etiology of deafness.

Etiological heterogeneity in diagnosis of syndromic deafness was observed in the present study. The cases could be classified in twelve groups according to the mode of inheritance and associated anomalies caused by the same gene.

Group 1: Chromosomal syndrome and genetic hearing loss:

This group included only one patient (Nº: 1). He was mentally retarded and had the characteristic craniofacial features of Down syndrome. Chromosome analyses revealed a 47,XY + 21 karyotype of the standard trisomy 21. Hearing impairment was noticed around the age of 9 years. Audiometry revealed a bilateral asymmetrical right severe and left moderate, sensorineural type of
hearing loss. This type of hearing loss with variable severity is more common (2).

Chromosomal abnormalities account for a significant number of the common syndromes in which some degree of hearing loss occurs. The most important Chromosomal disorder is Down syndrome (11).

Prompt management is warranted as chronic hearing loss further impairs the learning ability of the Down syndrome child.

**Group 2: Dominant external ear malformation and genetic hearing loss:**

This group included only one patient (N° 2). The patient had microtia and meatal atresia. Audiometry showed conductive hearing loss with speech discrimination. This condition was previously reported (11,12). The patient was the only affected member in his family and the only offspring of non-consanguineous parents. Although it is likely that the syndrome is transmitted in an autosomal recessive manner (12), dominant inheritance was supported (13) which was then confirmed (14).

**Group 3: Hereditary musculo skeletal involvement and genetic hearing loss:**

The manifestations of distal arthrogryposis (15) were declared in patient N° 3. Hearing impairment was noticed in childhood. Audiometry showed bilateral symmetrical sensorineural hearing loss with speech discrimination. The cousin of the patient had the same manifestations but in severe form. There was a family history of equinovarus deformity, club foot / or bowing off legs. Hence polygenic mode of inheritance is suggested.

**Group 4: Dominant ocular disorders and genetic hearing loss:**

This group included two patients (N° 4 and 5). Patient N° 4 had optic atrophy. He presented by ataxia and deafness. Audiometry revealed sensorineural hearing loss of moderate severity at low frequency. His father had the same manifestations at earlier age. The condition was progressive until he became completely deaf and blind. These findings in father and his son were previously reported (16). Consequently this case was diagnosed as dominantly inherited type of deafness associated with optic atrophy.

Patient N° 5 had hearing impairment during infancy. Audiometry revealed a bilateral symmetrical moderate sensorineural hearing loss with poor speech discrimination. The clinical findings of progressive myopia, deafness, flat facial appearance and few manifestations of joint involvement were suggestive of autosomal dominant Stickler syndrome (17). Two older sibs of the proband developed ocular problems and deafness without manifestation of arthritis, suggesting the dominantly inherited “Wagner syndrome”. It was reported that Wagner syndrome may have overlapping features with Stickler syndrome (18). So “Stickler – Wagner syndrome” was suggested as a diagnosis for such cases, with autosomal dominant inheritance and highly variable expressivity.

**Group 5: Recessive ocular disorders and genetic hearing loss:**

Two female sibs, of consanguineous parents, were included in this group (patient N° 6, 7). They had hearing impairment in early infancy. Audiometry of both revealed a congenital bilateral symmetrical severe to profound sensorineural deafness. Later on they developed visual loss due to retinitis pigmentosa. On the basis of the clinical findings in the two sisters, they were considered as variants of Usher syndrome. Genetic heterogeneity (19,20) provides the possible explanation for the clinical variation which is expressed in the level of hearing loss and extent of fundal pigmentary changes.

Usher syndrome is a clinically and genetically heterogeneous disorder characterized by profound congenital hearing loss combined with retinitis pigmentosa. This dual sensorineural deficiency is transmitted in an autosomal recessive mode. Usher syndrome is recognized as the most frequent (3%) cause of hereditary deaf-blindness (21).

Patient N° 6 showed associated manifestation of albinism. Also several family members showed the manifestation of albinism. Pedigree analysis suggested that the two autosomally recessive disorders (Usher syndrome and albinism) were inherited as two separate entities in this patient (figure 1). The parental consanguinity has contributed to the aggregation of the recessive genes responsible for each disorder separately.

**Group 6: Dominant integumentary disorder and genetic hearing loss:**

This group included two patient (N° 8 and 9), they showed the manifestation of Waardenburg syndrome (WS). It is the most frequent (2%) form of congenital deafness in humans. It is caused by autosomal dominant mutation. Waardenburg syndrome have been categorized into several types: WS I, type II, III and IV. All these forms show marked variability in expressivity even within families (22). Hearing impairment in both patients was noticed during the first year of life. Audiometry of both
patients revealed congenital bilateral symmetrical sensorineural deafness affect all frequencies.

Patient No. 8 was diagnosed as WS type II. She was the first case to appear in her family of non-consanguineous parents as a result of new mutation.

Patient No. 9, the offspring of non-consanguineous parents, showed the manifestations of WS type I. Pedigree analysis revealed that most of the proband's relatives in four generations, including his father and his sibs, showed the manifestation of WS type I with associated deafness but they were not available for examination (figure 2). Incomplete penetrance and variable expressivity of the dominant gene explains the variability of the WS characteristics in most patients (23).

Patient No. 9 was born with myelomeningocele, his older brother was born with the same defect and he had also the manifestation of WS type I. The first family in which more than one subject was affected with both WS and myelomeningocele was reported (24). The report declared that it is possible that a genetic susceptibility locus for myelomeningocele is located near the gene for WS type I and the association is related to a contiguous gene syndrome rather than pleiotropy. A deletion in this region could then produce both disorders.

Recently it has been reported that genetic background in combination with PAX 3 allele, a transcription factor expressed during embryonic development, may be important factors in the etiology of deafness in WS (25). Restituted with permission.

Group 7: Recessive neurological disorders and genetic hearing loss:

This group included two patients, sibs No. 10 and 11. Hearing impairment was noticed during the first year of life in both sibs. Audiometry revealed a congenital bilateral symmetrical sensorineural type with increasing impairment at high frequencies in both sibs.

Clinical examination and motor conduction velocities suggested the diagnosis of hereditary motors sensory neuropathy “Charcot–Marie–Tooth” type I in the two sibs (26). No fundal abnormality was detected in both sibs. Charcot–Marie–Tooth (CMT) disease can be inherited either dominantly, or recessively, or linked to the X chromosome (27). Recently it has been found that CMT type I, an autosomal dominant, is often associated with a duplication in p 11.2 region of chromosome 17 (28).

The combination of CMT and deafness in the two sibs in the present study, who are offspring of consanguineous unaffected parents (first cousins), suggesting a recessive mode of inheritance as reported by other investigators (29).

Group 8: Hereditary renal dysfunction and genetic hearing loss:

This group included three male patients No. 12, 13 and 14. They were sibs aged 12, 16 and 19 years respectively. They developed persistent microscopic hematuria and proteinuria that progress to renal failure in deaf patients. So they were diagnosed as having Alport syndrome (30).

Hearing impairment was developed early during infancy in patients No. 12 and 13. Their older brother (No. 14) developed hearing impairment during adulthood. Audiometry of the present patients revealed bilateral symmetrical sensorineural hearing loss affecting the high frequencies with a severe degree in patient No. 14, mid and high frequencies with moderate degree in patient No. 12, and all frequencies with profound degree in patient No. 13. Gubler et al (1981) (30) concluded that hearing loss in Alport syndrome is never congenital, but often can be detected before the age of 10 years.

The present study was extended including the parents and two sisters of the probands aged 10 and 9 years respectively. These two girls showed mild renal symptoms. Audiometry revealed normal hearing in both. Their mother showed a mild hearing impairment. Their father was normal as regards renal and audiometric investigations.

Pedigree analysis document genetic heterogeneity (31) with autosomal dominant and X-linked forms. The autosomal dominant inheritance of maternal origin is possible as their grandmother died from renal failure and their mother showed some manifestations of the syndrome, but not severe as there sons (probands). This difference in severity between males and females is well known in this syndrome. X – linked inheritance is also possible with manifesting carrier females. Autosomal recessive inheritance cannot be excluded due to parental consanguinity, but its possibility is not strongly suggested as the autosomal dominant and X – linked modes of inheritance.

Group 9: Recessive metabolic dysfunction and genetic hearing loss:

This group included five patients, No. 15 – 19; they had goiter with variable degrees. Goiter was noticed before the age of 5 years. The patients were euthyroid on estimation of thyroxine hormone (T4). Hearing loss was congenital bilateral symmetrical profound sensorineural in the patients No. 15, 16 and 17 (sibs), moderate to severe in patient No. 18, and right moderate to severe and left...
severe profound in patient N: 19. This hearing loss affects high frequencies in all patients. These findings have been described in Pendred syndrome (32), hence these patients were given this diagnosis.

Pendred syndrome is the association between congenital and sensorineural deafness and goitre. This syndrome is inherited as an autosomal recessive trait and has been mapped to chromosome 7 q 31 (33). A deficiency in the peroxidase enzyme system in the labyrinth would be expected to be responsible for hearing loss in Pendred syndrome (14).

Pedigree analysis of the patients in present study revealed that all the patients were offspring of unaffected consanguineous parents (first cousins) and the syndrome occurred among sibs. Thus the mode of inheritance is autosomal recessive.

**Group 10: X-linked metabolic dysfunction and genetic hearing loss:**

This group included three male patients, N: 20, 21, and 22. Their ages ranged between 4 and 6 years. They showed the clinical features of Hunter syndrome. Patient N: 20 had more severe form of features and severe mental retardation. Patients N: 21 and 22 had mild mental retardation. Biochemical screening of the urine was positive for mucopolysaccharides. Identification of this excreted mucopolysaccharides by thin layer chromatography revealed both dermatan and heparan sulphate. Audiometry of the three patients revealed mixed hearing loss affecting all frequencies.

Two types of Hunter syndrome are distinguished (14), type A has mild form and type B has severe form with progressive mental retardation. Accordingly, patient N: 20 was diagnosed as Hunter syndrome type B (MPIIB), while patients N: 21 and 22 were diagnosed as Hunter syndrome type A (MPIIA).

Hunter disease is an X-linked recessive mucopolysaccharide storage disorder and is rare in families (34). The inheritance of MPII as an X-linked recessive genetic disorder is consistent with the diagnosis of the three boys in the present study.

**Group 11: Indefinite diagnosis:**

Hearing impairment was noticed in male patient N: 23 during the first few months of life. Audiometry revealed a congenital bilateral asymmetric, right severe, and left moderately severe, sensorineural hearing loss. An accurate diagnosis could not be reached in this patient. The presence of retinal pigment motting, with the absence of night blindness, and sensorineural deafness may suggest the autosomal recessive syndrome of “inverse retinitis pigmentosa.

sensorineural deafness and hypogonadism” (35). Hypogonadism could not be assessed as the proband was 3 years old. On the other hand, the presence of prominent nasal root, isochromia iridis with mottled pigment deposits and sensorineural deafness with hypopigmented area which is nearly like café au lait patch on the left side of the trunk may suggest “Waardenburg syndrome type II” as a new mutation (36).

**Group 12: Idiopathic deafness:**

This group included two cases N: 24 and 25. Patient N: 24, a female aged 7 years, had mild mental retardation. Audiometry revealed a congenital bilateral symmetrical moderate sensorineural type of hearing loss. The patient was born with congenital giant pigmented nevus occupying most of the face and smaller ones along the upper and lower limbs and on the back. Clinical and histopathological criteria of the nevus are consistent with those of the giant pigmented hairy nevus (37). Fundus examination and CT scan of the brain showed normal fundi and normal brain scan, which were not consistent with neurocutaneous melanosis as a diagnosis. The patient was the only affected case in her family, i.e. sporadic, of non-consanguineous parents. This suggested that her condition is the result of a new mutation (38).

The other male patient N: 25, aged 4 years, had congenital bilateral symmetrical profound sensorineural hearing loss affecting all frequencies. The patient showed abnormal position of arm movement, which was confirmed radiologically by proximal radio-ulnar synostosis. Macrocephaly and cryptorchidism were also detected. Fundus examination revealed no abnormality. CT scan of the brain suggested the possibility of low grade hydrocephalic changes. Radio-ulnar synostosis is seen in a number of chromosomal syndromes, particularly those involving abnormal number of x and y chromosomes (15). This was excluded in the present proband by chromosomal analysis that revealed a normal male karyotype. After careful research of the literature, the combination of radio-ulnar synostosis, mild hydrocephalus, and cryptorchidism with congenital sensorineural type of hearing loss was not previously mentioned.

The proband was the first case to appear in his family of consanguineous parents (first cousins). His condition is most probably inherited in an autosomal recessive manner.

In conclusion, the assessment of a child with syndromic hearing loss is complex and requires the interaction of audiologist, geneticist, and ophthalmologist for accurate diagnosis of the
precise genetic cause of hearing loss. Syndromic hearing loss is quite heterogeneous at the phenotypic level. Thorough clinical examination and complete investigations were the main criteria for accurate diagnosis. Determination of the pattern of transmission is essential to provide genetic counseling for the parents of a deaf child.
Fig. 1: Pedigree of patients 6 and 7 with Usher syndrome. Note separate inheritance of both recessive conditions (Usher syndrome and Albinism).

Fig. 2: Pedigree of patient 9 with WS, type I showing the dominant pattern, of transmission of the syndrome in four generations with variable expression.
References


