"Le Ipoacusie Genetiche: studio clinico e genetico molecolare delle forme sindromiche e non sindromiche"

collaborazioni

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WHAT IS ALREADY KNOWN….

Deafness is the commonest condition affecting the senses, with an incidence of 1 -2 cases out of every 1.000 births. It can be classified as neurosensorial, transmissive or mixed; syndromic, if it is associated with other signs or clinical symptoms or non-syndromic; pre-speech or post-speech if it appears before or after the ability to speak.

In recent years the analysis of deafness has become increasingly important in the study of congenital defects because of the far-reaching repercussions in the social environment; late recognition early on in development determines serious delays in the ability to speak and in the child's learning process.

WHAT IS ALREADY KNOWN….

From the pathogenetic point of view deafness has various causes: environmental, like traumas, infections, medicines and genetic, the latter of which is responsible for approximately 60 to 70% of deafness cases. So far, at least 39 genes have been identified, which, if they mutated, can determine this pathology; amongst the non-syndromic forms (NSHL) the gene which is most frequently involved is connexin 26, which is responsible for about 50% of cases.

WHAT THE PROJECT ADDS TO…

In 2006 we studied a group made up of 164 patients predominantly on pediatric age who had been referred to plan cochlear implant and/or to ascertain the causes of the hearing loss from 1993 to 2006. We applied a systematic protocol, which was used to assess the causes of this so heterogeneous condition. Our studies showed that most cases (61%) of infantile deafness could be attributed to genetic reasons, of which 32% are syndromic and 29% non-syndromic, followed by 21% of cryptogenetic cases.

WHAT THE PROJECT ADDS TO…

We found a higher incidence of syndromic cases than the literature suggested, thus confirming the importance of the clinical genetic evaluation and of the collaboration with the various specialists. From a study on a wider scale a systematic protocol both for the assessment of syndromic and non-syndromic hearing loss could emerge which could be applied on national level.

Table 1: Protocol applied during genetic examination to children with suspected deafness or family history positive for deafness.

GENETIC DEAFNESS PROTOCOL

PRENATAL ANAMNESIS

Infectious diseases maternal or in cohabitants, pharmacological therapies, ultrasound monitoring, complications of pregnancy, modalities of delivery

PERINATAL ANAMNESIS

Perinatal asphyxia, Apgar score, weight at birth, neonatal icterus

POSTNATAL EVENTS

Psycomotor development, infectious diseases (meningitis), concussion, otitis, adenoidal hypertrophy, tinnitus, nystagmus, therapies with ototoxic drugs

AGE AND CIRCUMSTANCES AT FIRST SUSPICION OF DEAFNESS

LANGUAGE EVALUATION

DRAWING OF FAMILY TREE

Consanguinity, parents' age at time of conception, deafness, thyroid, kidney and eye diseases

Table 1: Protocol applied during genetic examination to children with suspected deafness or family history positive for deafness.

GENETIC DEAFNESS PROTOCOL

PHYSICAL EXAMINATION

Anthropometric and craniometric (craniosynostosis) findings, intercantal and interpupillar distances, research of iris heterocromy and blue sclera, dimensions of eye, dimensions and morphology of ear (lop ear, preauricolar appendix and fistula), cleft palate and dental anomalies (enamel dysplasia, conoid teeth)

Neck: exclude Klippel-Feil and value thyroid

Heart: auscultation

Cutis: anomalies of cutis and hair pigmentation, atopy

Hands and feet: syndactyly, polydactyly, onicodystrophy

LABORATORY AND INSTRUMENTAL TESTS

Urine analysis, TORCH complex, FT3, FT4, TSH, CPK, cholinesterase, APTT, PT, molecular analysis for connexin 26 and 30 and for principal mitochondrial mutations (especially in cases with onset before 5 years, with bilateral deafness), kidney and thyroid ultrasound, cardiological examination, ECG, ophthalmologic examination with fundus and examination with fessura lamp (research of retinopathies, issues of chorioretinitis, optic nerve atrophy, cataract). Audiometry and evaluation of impedance, otoemissions, ABR, Computerized axial Tomography and MRI for middle and internal ear.

I. NORMAL OR SUBNORMAL HEARING (0-20 dB HL)
The average tone loss is below 20 dB.
Mild tone disorder with no social consequences.

II. MILD HEARING LOSS (21-40 dB HL)
Average tone loss between 21 and 40 dB.
Speech is perceived if the voice is normal, difficulties arise if the voice is low-pitched or distant
from the subject. Most daily life noises are perceived.

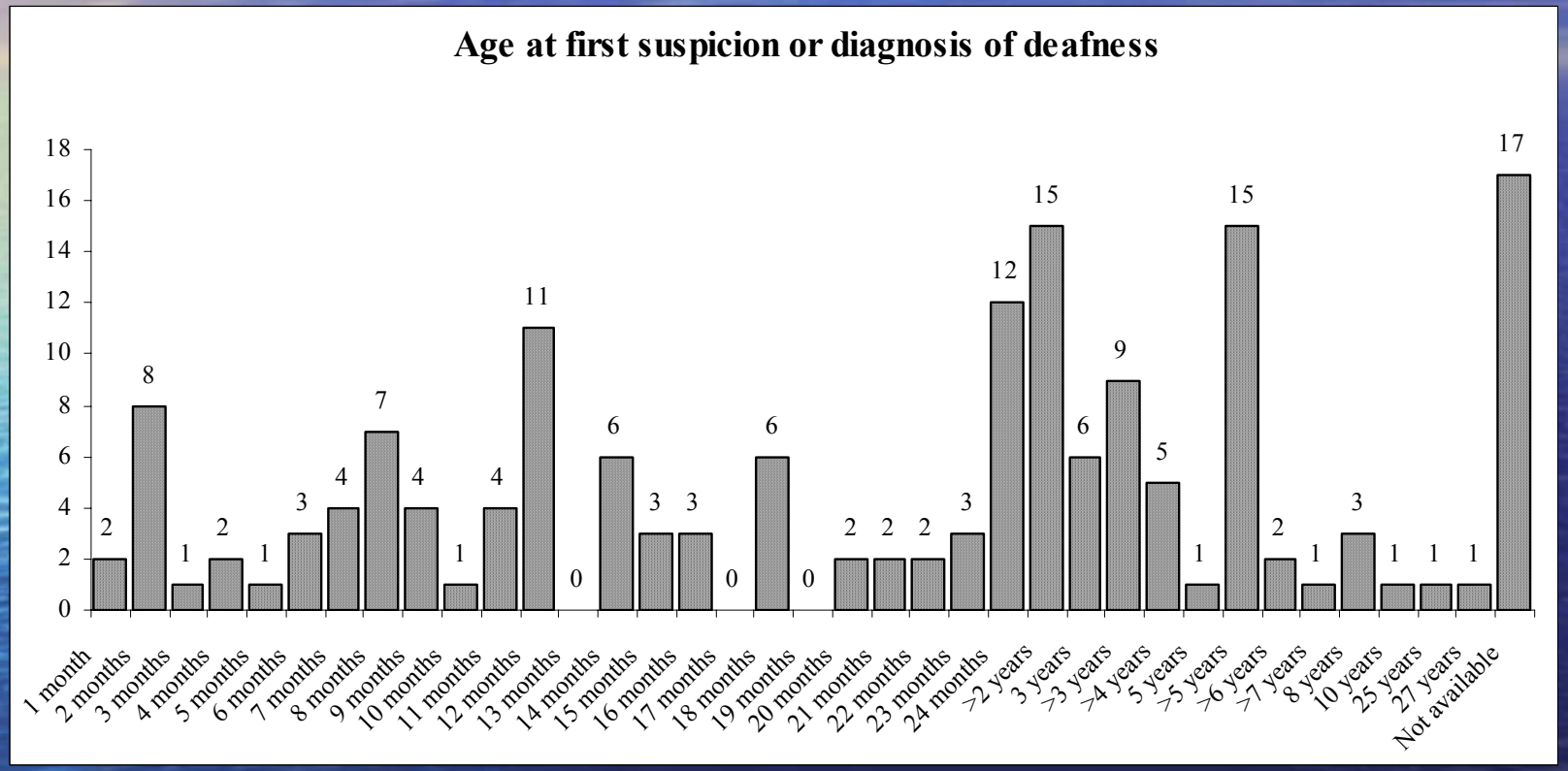
III. MODERATE TO SEVERE HEARING LOSS (41-70 dB HL)
1st degree: average tone loss between 41 and 55 dB.
2nd degree: average tone loss between 56 and 70 dB.
Speech is perceived if the voice is loud. The subject understands better what is being said if he
can see his/her interlocutor. Some daily life noises are still perceived.

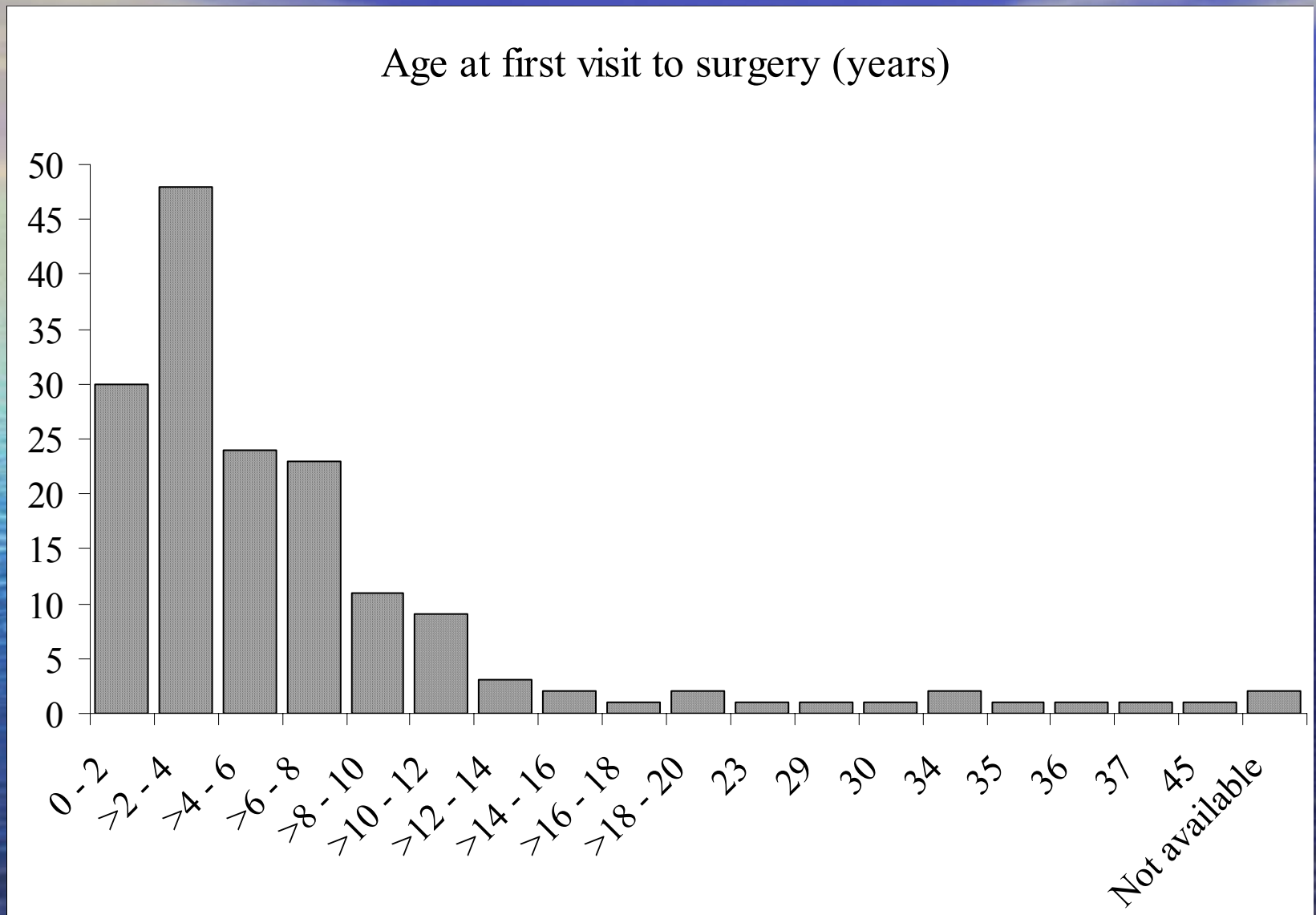
IV. SEVERE HEARING LOSS (71-90 dB HL)
1st degree: average tone loss between 71 and 80 dB.
2nd degree: average tone loss between 81 and 90 dB.
Speech is perceived if the voice is loud and close to the ear. Loud noises are perceived.

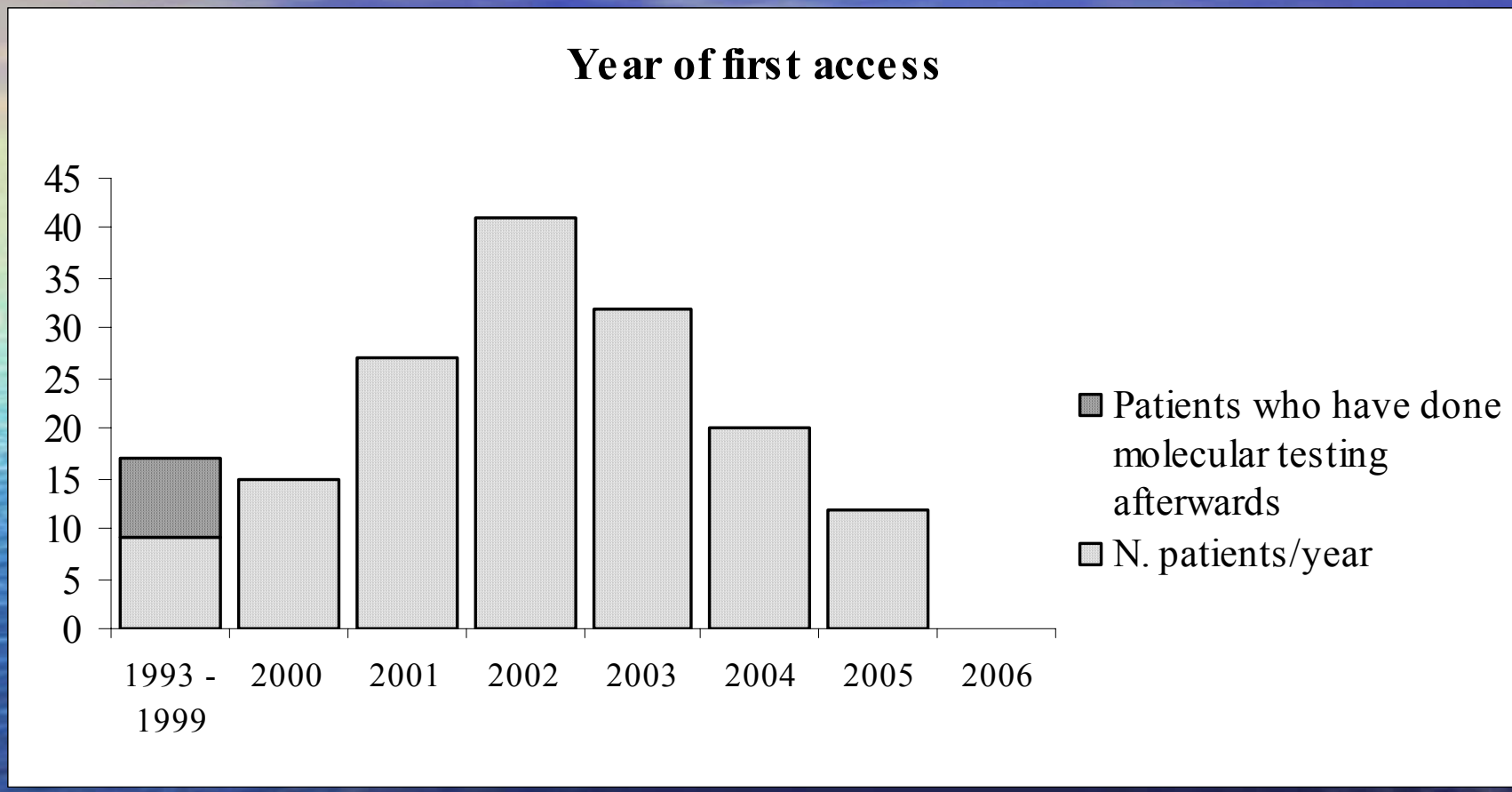
V. PROFOUND HEARING LOSS (91-119 dB HL)
1st degree: average tone loss between 91 and 100 dB.
2nd degree: average tone loss between 101 and 110 dB.
3rd degree: average tone loss between 111 and 119 dB. Speech is not perceived. Only very loud
noises are perceived.

VI. TOTAL HEARING LOSS. COPHOSIS (120 dB)
Average tone loss over 120 dB. Nothing is perceived.

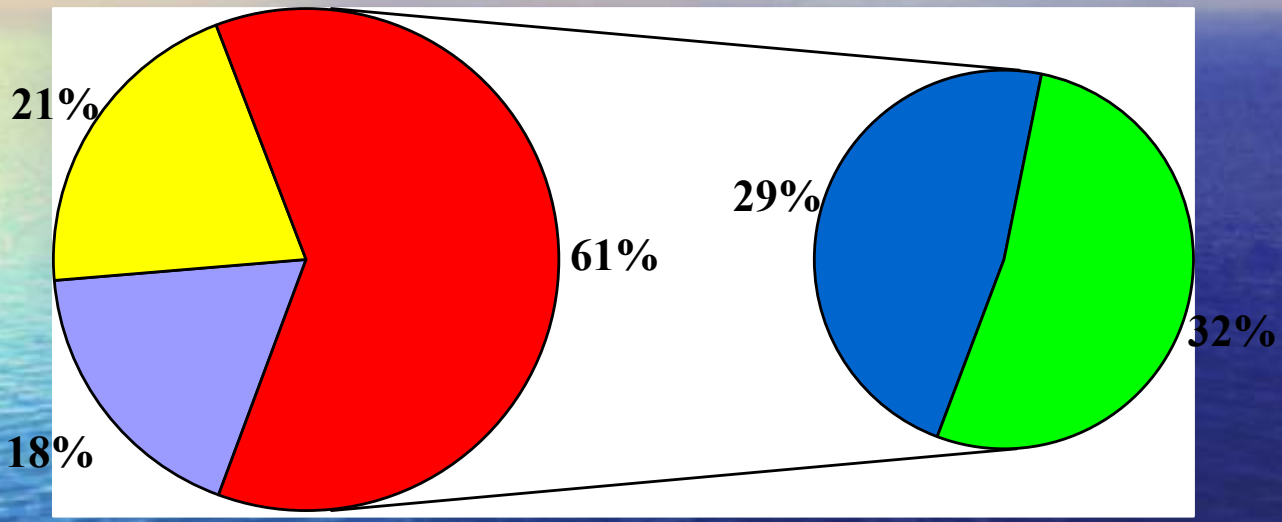
Fig. 1: Age at first suspicion or diagnosis of deafness.




Age at first visit to surgery (years)
50
45
40
35
30
25
20
15
10
5
0
0 - 2
>2 - 4
>4 - 6
>6 - 8
>8 - 10
>10 - 12
>12 - 14
>14 - 16
>16 - 18
>18 - 20
23
29
30
34
35
36
37
45
Not available


Year of first access
45
40
35
30
25
20
15
10
5
0
1993 - 1999
2000
2001
2002
2003
2004
2005
2006
Patients who have done molecular testing afterwards
N. patients/year

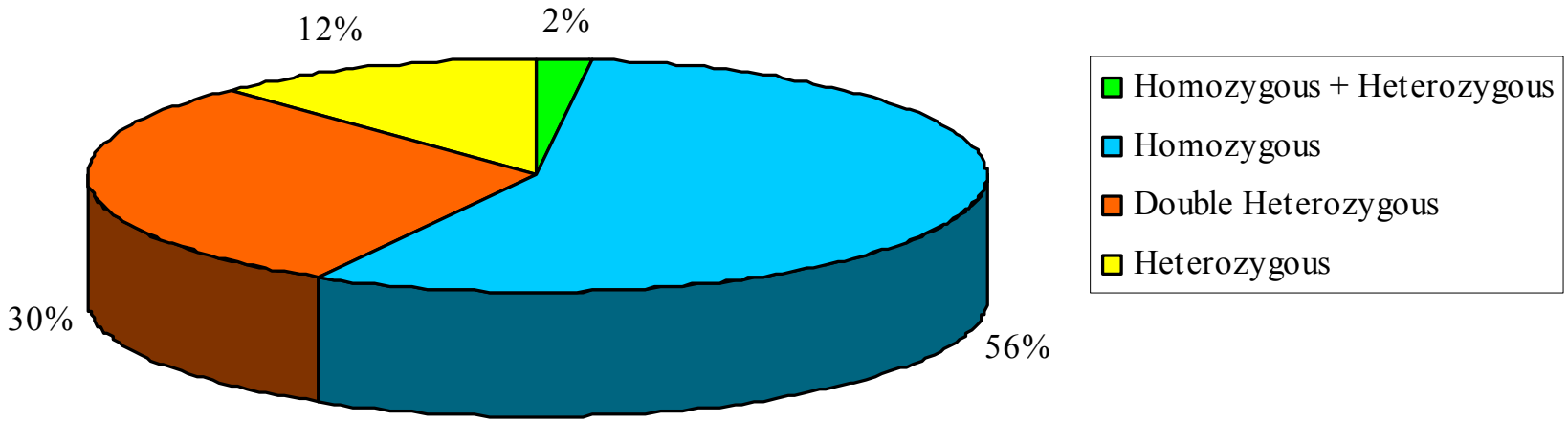
Country of origin (in alphabetic order)	Patient No.
AFRICA (not better precised)	2
ECUADOR	1
INDIA	1
MOROCCO	3
PAKISTAN	1
ROMANIA	1
SLOVENIA	1 (mother)
SLOVENIA / ALBANIA	2
TUNISIA	2 (sisters)


21%
61%
18%
29%
32%
ACQUIRED
CRYPTOGENETIC OR UNKNOWN
GENETIC DEAFNESS WITHOUT ASSOCIATED ANOMALIES
KNOWN GENETIC SYNDROMES

Hearing impairment etiology	Suspect/Clinica diagnosis	Molecular confirmation
GENETIC	100 (60,98%)	48
NON SYNDROMIC	48 (29,27%)	4
SYNDROMIC	52 (31,71%)	3
Syndromic AD	21 (12,80%)	1
Waardenburg syndrome	13 (7,93%)	0
Waardenburg syndrome type I	5 (3,05%)	Under testing
Waardenburg syndrome type II	8 (4,88%)	2
BOR syndrome (branchio-oto-renal)	1 (0,61%)	Under testing
Stickler syndrome	2 (1,22%)	2
Piebaldism form AD	1 (0,61%)	Under testing
Deletion Cr.22 syndrome (del22q11)	3 (1,83%)	Under testing
Oculo-dento-digital syndrome	1 (0,61%)	2
Syndromic AR	13 (7,93%)	
Pendred syndrome	7 (4,27%)	
Usher syndrome	5 (3,05%)	
MCA/MR syndrome not specified	1 (0,61%)	
Syndromic X-Linked	1 (0,61%)	
Opitz G/BBB syndrome	1 (0,61%)	
Other syndroms and congenital anomalies	17 (10,37%)	
Wildervanck syndrome	1 (0,61%)	
Goldenhar syndrome	6 (3,66%)	
Myhre syndrome	1 (0,61%)	
Otosclerosis	1 (0,61%)	
CHARGE association	2 (1,22%)	
Microtia	3 (1,83%)	
Microcephaly	2 (1,22%)	
Cleft Palate	1 (0,61%)	

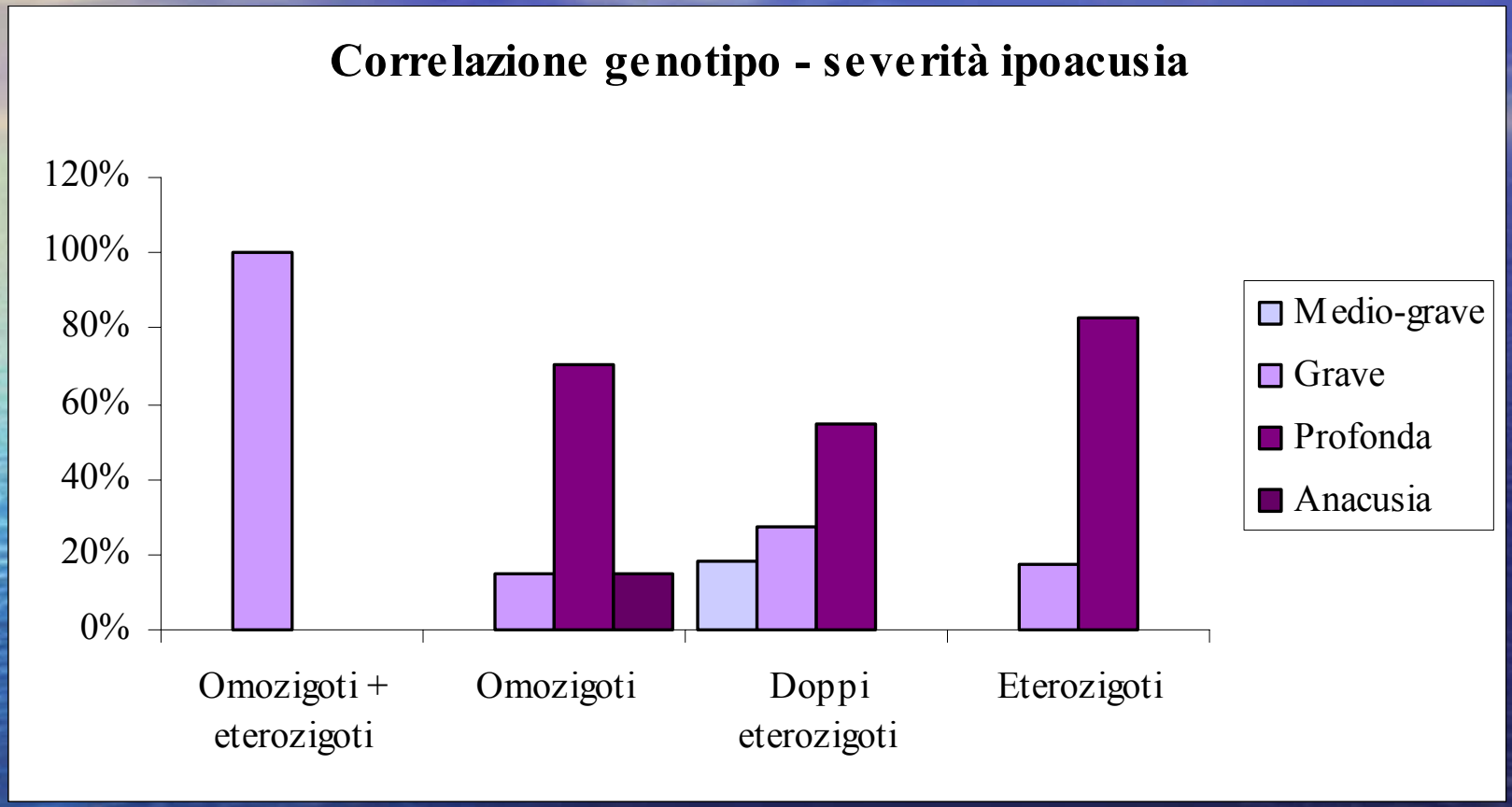
UNKNOWN (CRYPTOGENETIC)	34 (20,73%)	-
PRENATAL CONGENITAL INFECTIONS Rubella Cytomegalovirus (CMV) Toxoplasma Other	9 (5,49%) 9 (5,49%) 3 (1,83%) 3 (1,83%) 1 (0,61%) 2 (1,22%)	-
PERINATAL NEONATAL SEPSIS PERINATAL SUFFERING Acute foetal suffering Oligohydramnios PREMATURITY	19 (11,59%) 1 (0,61%) 4 (2,44%) 2 (1,22%) 2 (1,22%) 14 (8,54%)	-
POSTNATAL MENINGITIS	2 (1,22%) 2 (1,22%)	-

Mutation distribution



HOMOZYGOUS + HETEROZYGOUS	1
L90P/L90P + delE120	1
HOMOZYGOUS	28
35delG/35delG	26 (2 brothers; 2 sisters)
W24X/W24X	2 (2 sisters)
DOUBLE HETEROZYGOUS	15
35delG/W133X(novel)	2
35delG/E47X	2
35delG/-3170G→A	2
35delG/35insG	2 (2 brothers)
35delG/delE120	1
35delG/V95M	1
35delG/R184W	1
35delG/290-291insA	1
35delG/L90P	1
35delG/A40G	1
167delT/del(GJB6-D13S1830)	1
HETEROZYGOUS	6
W133X (novel)	1
167delT	1
V153I (polymorphism)	1
M34T (polymorphism)	1
V156I (novel)	1

FREQUENCY SPECTRUM		
Mutation	Frequency	Frequency %
35delG (Cx26)	66	69,47%
W24X (Cx26)	4	4,21%
L90P (Cx26)	3	3,16%
delE120 (Cx26)	2	2,11%
W133X (Cx26) (novel)	2	2,11%
E47X (Cx26)	2	2,11%
-3170G→A (Cx26)	2	2,11%
35insG (Cx26)	2	2,11%
167delT (Cx26)	2	2,11%
V153I (Cx26) polymorphism	2	2,11%
V95M (Cx26)	1	1,05%
R184W (Cx26)	1	1,05%
290-291insA (Cx26)	1	1,05%
A40G (Cx26)	1	1,05%
M34T (Cx26) polymorphism	1	1,05%
V156I (Cx26) novel	1	1,05%
G224A (Cx26) novel	1	1,05%
del(GJB6-D13S1830) (Cx30)	1	1,05%
Total	95	100,00%


Correlazione genotipo - severità ipoacusia
120%
100%
80%
60%
40%
20%
0%
Omozigoti + eterozigoti
Omozigoti
Doppi eterozigoti
Eterozigoti
Medio-grave
Grave
Profonda
Anacusia

Hearing impairment etiology	Dereymaeker *(Belgium, 1991)*	Kiese-Himmel *(Germany, 1997)*	Walch *(Austria, 2000)*	Morzaria *(Canada, 2004)*	Silan *(Turkey, 2004)*	Riga *(Greece, 2005)*	Own results *(Italy, 2006)*
GENETIC	27,57%	34,2%	f. 18%	30,7%	62,90%	48%	60,98%
Non syndromic	23,77%	f. 15,9%	-	27,2%	44,90%	36%	29,27%
Syndromic	3,80%	18,3%	-	3,5%	18,00%	11%	31,71%
UNKNOWN	27,09%	38,6%	44%	41,5%	17,63%	15%	20,73%
ACQUIRED	45,34%	27,3%	38%	27,8%	19,45%	38%	18,29%
Prenatal	18,46%	2,3%	7%	11,5%	2,18%	-	5,49%
Perinatal	12,15%	11,4%	20%	9,7%	1,46%	-	11,59%
Postnatal	14,73%	13,6%	11%	6,6%	15,81%	-	1,22%

PROJECT'S MAIN OBJECTIVE

1) The main objective is to work on final clinical and diagnostic shared protocol on genetic deafness which esamines both the NSNHLs and syndromic forms; such a protocol does not exist for the moment in Italy. The protocol which would come from a study carried out systematically could be applied nationally since it would be planned specifically on the situation in our country as opposed to that of other states. The application of this protocol with the aim of a correct diagnosis is directed at improving the health of the child suffering from hearing loss has great advantages from a diagnostic, rehabilitative point of view, as well as prevention of complications. In addition, there are undoubted advantages for the family, which can be offered appropriate genetic counselling.