Severe to profound deafness may be associated with MYH9-related disease: report of 4 patients

La sordità da severa a profonda può essere associata alla malattia MYH9-correlata: report di 4 pazienti

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SUMMARY

MYH9-related disease (MYH9-RD) is a rare genetic syndromic disorder characterised by congenital thrombocytopenia and is associated with the risk of developing progressive sensorineural hearing loss, nephropathy and presenile cataracts during childhood or adult life. All consecutive patients enrolled in the Italian Registry for MYH9-RD with severe to profound deafness were included in a retrospective study. The study population involved 147 Italian patients with MYH9-RD: hearing loss was identified in 52% of cases and only 4 patients (6%) presented severe to profound deafness at a mean age of 33 years. Deafness was associated with mild spontaneous bleeding in all patients and with kidney involvement in 3 cases. Cochlear implantation was carried out in 3 cases with benefit, and no major complications were observed. Diagnosis was performed about 28 years after the first clinical manifestation of MYH9-RD, which was never suspected by an otolaryngologist. The clinical and diagnostic aspects of 4 patients with severe to profound deafness are discussed with a focus on therapeutic implications.

KEY WORDS: MYH9 • Hearing loss • Genetic syndrome

RIASSUNTO

La malattia MYH9-correlata è una rara sindrome genetica caratterizzata da piastrinopenia congenita associata al rischio di sviluppare, durante l'infanzia o l'età adulta, ipoacusia neurosensoriale, nefropatia e cataratta presenile ad andamento evolutivo. Furono inclusi in uno studio retrospettivo tutti i casi con sordità da severa a profonda arruolati consecutivamente nel Registro Italiano dei pazienti affetti da malattia MYH9-correlata. La popolazione esaminata coinvolse 147 pazienti Italiani con malattia MYH9-correlata: l'ipoacusia fu identificata nel 52% dei casi e solo 4 pazienti (6%) presentarono un quadro di sordità da severa a profonda all'età media di 33 anni. In tutti i 4 pazienti, la sordità fu associata ad un lieve sanguinamento spontaneo e in 3 pazienti fu accompagnata da un coinvolgimento renale. L'impianto cocleare fu eseguito in 3 casi, con beneficio, in assenza di complicanze maggiori. La diagnosi di malattia MYH9-correlata fu eseguita circa 28 anni dopo la prima manifestazione clinica della malattia che non fu mai sospettata da un otorinolaringoiatra. Saranno discussi gli aspetti clinici e diagnostici di 4 pazienti con sordità da severa a profonda affetti da malattia MYH)-correlata, focalizzando anche le implicazioni terapeutiche.

PAROLE CHIAVE: *MYH9 • Ipoacusia • Sindrome genetica*

Introduction

Over the last century, research and technology have progressively made advances related to deafness and hearing loss, which still remains the most frequent sensory disability in developed societies [1-4]. About 50% of cases with congenital sensorineural hearing loss can be attributed to a genetic cause, and epidemiological studies estimate that in a considerable proportion of "unknown deafness aetiology", genetic factors are extremely relevant with both diagnostic and therapeutic implications [3 5-10].

MYH9-related disease (MYH9-RD) is a rare autosomal-dominant syndromic disorder deriving from mutations in MYH9, the gene encoding for the heavy chain of non-muscle myosin IIA (NMMHC-IIA) [11 12]. NMMHC-IIA is expressed in most cell types and tissues and is involved in several processes requiring force and translocation, thus it is essential during cell motility, cytokinesis and maintenance of cell shape [13]. In the inner ear, NMMHC-IIA is extensively distributed in the sensory hair cells of the organ of Corti, as well as in the spiral ligament, spiral limbus, with only minimal expression within the spiral ganglion. All patients with MYH9-RD present since birth with thrombocytopenia and inclusions of NMMHC-IIA in leukocytes. During infancy or adult life, most MYH9-RD patients develop additional clinical manifestations: sensorineural hearing loss, proteinuric nephropathy often leading to end-stage renal failure, cataracts and/or alterations of

liver enzymes [14-16]. Each of these non-congenital manifestations can occur alone or can variably associate with the others [17]. MYH9-RD includes four syndromes that have been considered for many years as distinct disorders: May-Hegglin Anomaly, Sebastian syndrome, Fechtner syndrome and Epstein syndrome. After the identification of MYH9 as the gene responsible for all of these syndromes, analyses of large series of patients demonstrated that they actually represent some of the different possible clinical presentations of the same condition, for which the definition of MYH9-RD has been introduced [14 18 19]. Described in 60% of cases and in 36-71% of pedigrees, hearing loss is the most frequent non-congenital manifestation of MYH9-RD [20 21]. Hearing impairment is limited to high frequencies at clinical onset and in mild forms, but it progressively involves all frequencies in severe phenotypes. When hearing disability is present since childhood or adolescence, patients usually develop severe to profound deafness within the first decades of life [17 22 23].

Nowadays, a simple immunofluorescence assay on peripheral blood slides is available to identify patients with MYH9-RD [24 25]. When severe to profound deafness occurs, performing a proper etiological diagnosis of deafness may have implications for prognostic assessment, patient counselling and treatment. Given that MYH9 mutations primarily damage hair cells, the finding that most MYH9-RD patients have excellent cochlear implantation (CI) outcomes is consistent with the NMMHC-IIA expression pattern observed in animals [26]. A correct diagnosis of MYH9-RD may help surgical decision-making due to hearing benefits related to CI in this specific genetic disorder. In 2006, the Italian Registry for MYH9-RD was created and approved by the Institutional review board of the IRCCS Policlinico San Matteo Foundation, Pavia, Italy. The experience from the Italian Registry for MYH9-RD of patients with severe to profound deafness is discussed herein, focusing on clinical and diagnostic aspects.

Materials and methods

All consecutive patients enrolled in the Italian Registry for MYH9-RD with severe to profound deafness were included in this retrospective study. All patients underwent a multidisciplinary assessment comprising haematological, audiological, ophthalmologic and nephrological evaluations. Diagnosis of MYH9-RD was made on the basis of the identification of NMMHC-IIA leukocyte inclusions by immunofluorescence assay on peripheral blood slides and confirmed through the identification of the causative MYH9 mutation by molecular screening [24]. Basic audiological examination consisted of microscopic ear study, pure-tone audiometry, speech recognition score (SRS) using disyllabic word lists presented in quiet conditions, tympanometry and acoustic reflex tests (if necessary). Pure tone average (PTA) was calculated considering air

conduction thresholds at 0.5-1-2-4 KHz (PTA was higher than 70 dB HL in enrolled patients).

Severity of bleeding was classified according to the WHO bleeding score (BS) [17]:

- grade 0 = no bleeding;
- grade 1 = only cutaneous bleeding;
- grade 2 = mild blood loss;
- grade 3 = gross blood loss, requiring transfusion;
- grade 4 = debilitating blood loss, retinal or cerebral associated with fatality.

Results

The study population involved 147 Italian patients with MYH9-RD (mean age at the last evaluation: 36 years, standard deviation: 20). Altogether, 139 subjects underwent complete multidisciplinary evaluation. Hearing impairment was identified in 72 cases (52%). Of these, 7 presented mild hearing loss (10%) and 61 showed moderate hearing impairment (84%). The 4 patients with severe to profound deafness (6%) were included in this study. Hearing loss was initially limited to high frequencies and in more severe forms it involved the middle and the low frequencies. In the 72 patients with hearing impairment, the age at onset was homogeneously distributed along the first to sixth decades. In 3 of the 4 cases with severe to profound deafness, hearing loss developed in childhood or adolescence and became severe by the age of 30 years. The mean age of enrolled subjects was 40 years. Table I provides an overview of the basic clinical features. Of note, three patients had sporadic disease deriving from a de novo mutation localised in the N-terminal head domain of NMMHC-IIA. CI was suggested and performed in three patients; in one case CI was carried out before definitive molecular diagnosis of MYH9-RD. CI selection criteria included mean thresholds between 0.5-1-2 kHz > 75 dB HL with open-set SRS ≤ 50% in the best aided condition without lip reading according to Italian recommendations [27]. Figure 1 shows pure-tone audiometry before surgery (patients 1, 2 and 3) or during the last follow-up (patient 4). In all cases CI was safe and effective in improving the hearing ability, without any perioperative bleeding complications after prophylactic platelet transfusions [26]. The CI electrode array was inserted through the round window in all cases. CI outcomes were stable over time. Diagnosis of MYH9-RD was made from 14 to 41 years (mean: 28 years) after the first clinical presentation of disease symptoms. In no patients was clinical suspect raised by an otolaryngologist. The main medical history of each patient is summarised below.

Case 1

The patient was referred at the age of 12 years to a nephrology unit because of proteinuria and mild alteration of kidney function. On the same occasion, thrombocytope-

nia resulting in easy bruising and menorrhagia was also found. The kidney damage quickly progressed over the following years to end-stage renal disease requiring peritoneal dialysis. At the age of 21, the patient underwent a first kidney transplantation that was rejected; a second kidney transplantation was successfully performed at the age of 25. Diagnosis of MYH9-RD was made at the age of 26 and suspected by a nephrologist. Hearing impairment was referred from the age of 20. The first audiological evaluation performed at 22 years of age showed bilateral moderate symmetrical sensorineural hearing loss with recruitment (Metz test: positive). Hearing loss progressed to severe deafness two years later. The patient received benefit from bilateral hearing aids for about 12 years. At the age of 34 years, the patient no longer received sufficient benefit from hearing aids (Table I) and was successfully submitted to CI (SRS with CI and hearing aid: 100% at 50 dB, SRS with CI and without hearing aid: 100% at 60 dB). Post-CI follow-up was of 7 years. Preoperative temporal bone CT scan and MRI showed no anomalies.

Case 2

The patient was referred to a haematology unit at the age of 4 years because of severe thrombocytopenia and easy bruising. A diagnosis of acquired immune thrombocytopenia was made. The patient was therefore treated with several lines of immunosuppressive therapy without any improvements in platelet count; at the age of 12 splenectomy was performed, without benefit. Hearing loss was referred from the age of 20 and progressed to severe deafness by 32 years. Bilateral hearing aids were first used at 30 years: the first audiological evaluation revealed a moderate bilateral symmetrical sensorineural hearing loss with recruitment (Metz test: positive). At the age of 40 years, the patient developed profound hearing loss, proteinuria and chronic renal failure. A diagnostic hypothesis of MYH9-RD was raised by an internist 36 years after the first clinical presentation. Some months later the patient was submitted to CI with benefit: SRS with and without hearing aid in the non-implanted ear was 90% at 50 dB. Preoperative imaging (CT scan and MRI) revealed no anomalies. Hearing results were stable over time (last follow-up: 6 years). Residual hearing in the non-operated side was not useful despite the best aided conditions: a bilateral sequential CI was proposed, but the patient decided to wait.

Case 3

The patient was first referred at the age of 3 years for thrombocytopenia that was discovered because of prolonged bleeding after tonsillectomy. Hearing loss was noticed at the age 8 when he underwent audiometric evaluation that revealed mild bilateral sensorineural hearing defect. Hearing loss was quite asymmetrical (left ear worse than the right one). Consecutive imaging investiga-

tions (CT and MRI) did not show inner ear malformations or retrocochlear pathologies. The patient experienced progression of hearing loss during the following years; the first use of bilateral hearing aids was reported at 34 years when deafness was already severe. Of note, at 12 years a diagnosis of immune thrombocytopenia was established leading to a series of ineffective immunosuppressive treatments (including splenectomy and chronic immunosuppressive drugs) until the age of 21 when the patient refused any further therapies. CI was carried out in the left ear (worst side) at 43 years, one year before the diagnosis of MYH9-RD that was performed at 44 years by an internist. Bilateral sequential CI was carried out in the right ear two years later (SRS with bilateral CI was of 100% at 50 dB). Post-operative follow-up was for 6 years from the first CI.

Case 4

The patient was referred at the age of 35 for a history of thrombocytopenia, recurrent epistaxis and gum bleeding present from late childhood. A history of hearing impairment was also present from at least 3 years. Family history revealed that his mother also had chronic thrombocytopenia and hearing loss. On these bases, a diagnosis of MYH9-RD was suspected by an internist and successively confirmed (21 years after the onset of MYH9-RD symptoms). Audiometric examination at diagnosis revealed moderate bilateral symmetrical sensorineural deafness requiring bilateral hearing aids. Hearing loss progressed to severe deafness after 6 years and mostly involved medium-high frequencies than lower ones ("ski-slope" hearing loss – Fig. 1). During the last follow-up, hearing evaluation did not require CI according to Italian recommendations [27] (Table I). No signs of kidney impairment or cataract were present, whereas chronic elevation of transaminases was found.

Discussion

MYH9-RD is a rare autosomal dominant disorder characterised by congenital thrombocytopenia and characteristic leukocyte inclusions of the mutant protein associated with the risk of developing progressive sensorineural hearing loss, nephropathy, cataracts and/or liver enzyme alterations during childhood or adult life [12 15]. The spectrum of causative mutations of MYH9-RD consists in at least 45 different mutations that have been identified in more than 300 MYH9-RD unrelated families [15 17 28 34]. Of note, 35-40% of reported patients have sporadic disease caused by a de novo mutational event [15].

In the experience of the Italian Registry for MYH9-RD, 4 patients developed severe to profound deafness at a mean age of 33 years. The disease was inherited with a dominant pattern in only one subject, whereas three patients were sporadic cases. In 3 patients (case 1, 2 and 3),
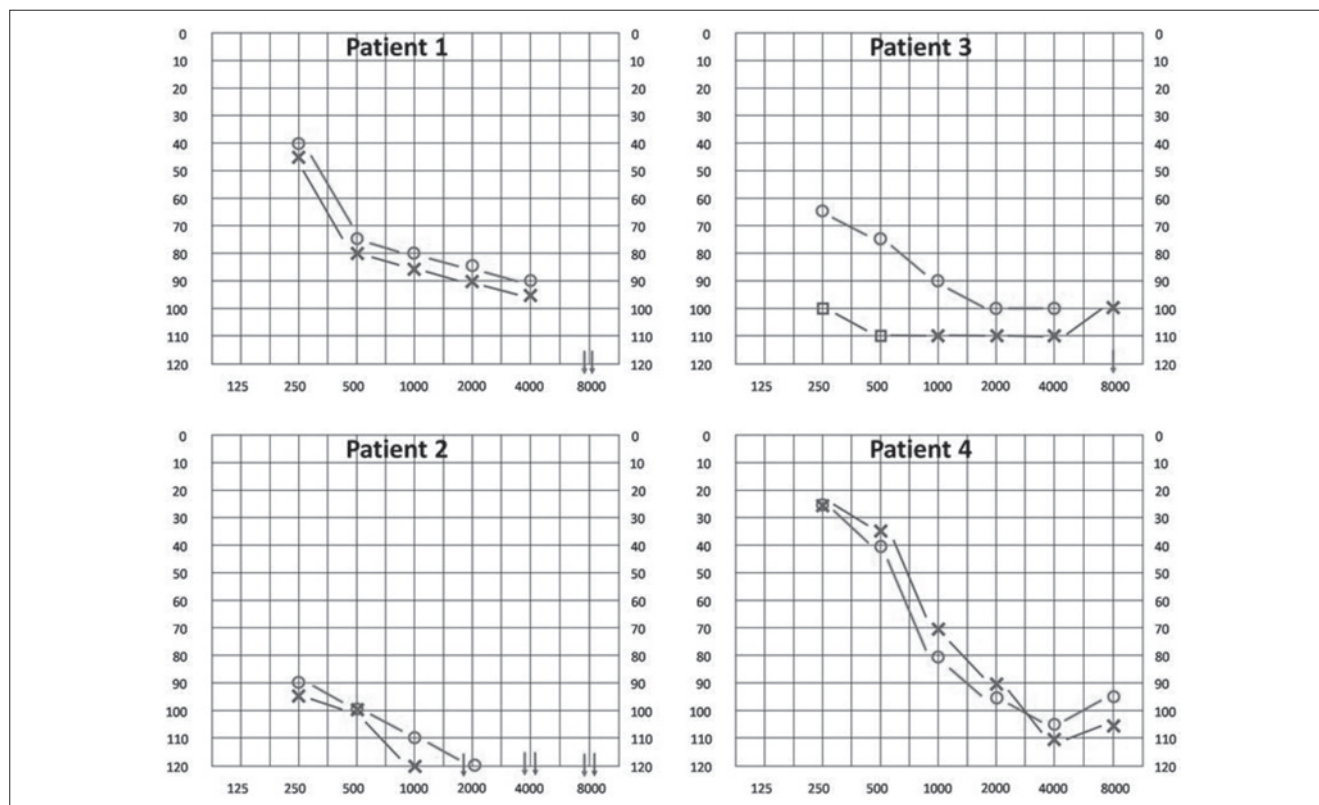
Fig. 1. Pure-tone audiometry before surgery (patients 1, 2 and 3) or during the last follow-up (patient 4).

the NMMHC-IIA mutation involved the N-terminal head domain: according to genotype-phenotype studies, these patients developed severe and early-onset deafness with severe kidney involvement [17 21]. Mutations in the C-terminal tail domain (case 4) show a low risk of developing severe hearing and kidney impairment: genetic or environmental factors probably interact with the MYH9 mutation leading to profound deafness and renal failure [17 21]. Deafness was clinically associated with mild spontaneous bleeding (grade 1 or 2 of WHO BS) in all patients and with kidney involvement (one case of kidney transplant) in three cases. Mean age at onset of hearing impairment was 21 years and severe to profound deafness occurred after a mean age of 11.5 years. Diagnosis was reached at a mean age of 36 years with a diagnostic delay of about 28 years after the first clinical manifestation of MYH9-RD. In no patients the clinical suspect was raised by an otolaryngologist, even if patients were submitted to audiological evaluations starting from a mean age of 24 years. Since the identification of the first MYH9 gene mutations, the number of MYH9-RD cases described in literature has greatly increased, particularly in Italy and Japan [24]. Even though diagnosis of MYH9-RD can be easily confirmed by a immunofluorescence screening test, it is often missed because it is not suspected [15 24]. Diagnostic difficulties derive from the poor awareness of the disease by physicians because of its rarity, heterogeneous MYH9-RD clinical presentation and the relative high frequency of sporadic patients who have negative family history. From the otolaryngologist's point of view, the association of bilateral sensorineural deafness with a personal or familiar history of thrombocytopenia, possibly associated with the other non-haematological manifestations of the disease, represents the key element for raising diagnostic suspicion of MYH9-RD. The literature highlights that 3-7% of patients with severe to profound deafness do not benefit from CI [8 9]. It has been hypothesised that patients with mutations causing spiral ganglion pathologies may show poor results in comparison with those ones involving hair cells [10 29]. The effectiveness of CI in MYH9-RD patients is strongly related to the localisation of NMMHC-IIA mutations in the sensory hair cells of the organ of Corti with only minimal involvement of the spiral ganglion [26]. During the last years, we are witnessing a rapid evolution in genetics with specific implications [5]. "Operate" without a diagnosis of disease may be debatable, and it also means the best management required with medical, legal and ethics implications is largely unknown.

Conclusions

According to the experience of the Italian Registry for MYH9-RD, hearing loss was observed in about half of cases, but severe to profound deafness was found in a limited percentage of subjects. When severe to profound

Table I. Basic clinical features and patients clinical presentation at diagnosis.

Patient /Family	Age/ Gender	Inheritance	NMMHC-IIA mutation (domain)	Bleeding diathesis (BS)	Platelet count (x 10⁹/L)	PTA right/left dB HL (SRS)	Tympanometry and acoustic reflex test	Kidney involvement	Cataract	Liver enzyme alterations
1/1	34/F	Sporadic	p.R702C (HD)	Easy bruising, menorrhagia (2)	14	82/87 dB HL (bilateral SRS < 50%)	Ty A, absent acoustic reflexes	Previous kidney transplantation	No	No
2/2	40/M	Sporadic	p.R702C (HD)	Easy bruising (1)	31	115/120 dB HL (bilateral SRS < 50%)	Ty A, absent acoustic reflexes	Nephrotic range proteinuria, chronic renal failure	No	Yes*
3/3	43/M	Sporadic	p.R702S (HD)	Epistaxis, easy bruising (2) Bleeding after tonsillectomy and tooth extractions (2)	25	91/110 dB HL (bilateral SRS < 50%)	Ty A, absent acoustic reflexes	Proteinuria	No	No
4/4	43/M	Autosomal-dominant	D1447V (TD)	Gingival bleeding (2)	48	80/76 dB HL (bilateral SRS > 50%)	Ty A, absent acoustic reflexes	No	No	Yes

Patient/Family= patient number and belonging family
Age/Gender= age at Italian Registry enrolment/gender.
Inheritance= type of inheritance of the MYH9-RD: sporadic ("de novo" mutation) or autosomal-dominant
NMMHC-IIA mutation (domain)= type of MYH9 gene mutation (domain involved: N-terminal head domain (HD), or C-terminal tail domain (TD))
Bleeding diathesis (BS)= bleeding symptoms (severity of bleeding according to the WHO bleeding score)[17]
Platelet count x 10⁹/L = platelet count measured by phase-contrast microscopy
PTA right/left (SRS)= Pure tone average calculated considering air conduction thresholds at 0.5-1-2-4 KHz before CI when performed or during the last follow-up (open-set speech recognition score in the best aided quiet condition without lip reading)
Tympanometry and acoustic reflex test= type of tympanogram according to Jerger's classification, present or absent acoustic reflexes
Kidney involvement= kidney damage developed
Liver enzyme alterations= liver involvement. *Patient with HCV hepatitis

deafness occurred, kidney involvement was present in almost all cases according to the genotype-phenotype correlation. When bilateral sensorineural hearing loss is associated with a personal or family history of thrombocytopenia and/or kidney involvement, MYH9-RD should be suspected.

Acknowledgements

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