Contribution of the Roman School to Vestibology

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Abstract
The experience of the Otolaryngology Clinic of Sapienza University of Rome over the past sixty years in the field of vestibular disorders is presented. From the beginning with the introduction of glycerol in the treatment of Meniere's disease, the scientific path of the research conducted is discussed, highlighting the acquisitions made to advance knowledge.

Introduction

The Polyclinic of Rome, named after King Umberto I, founded in 1903, was the first hospital built according to the innovative criteria of the time. It was well received by the Roman population and gradually expanded its influence throughout the region and surrounding areas. In this context, a significant number and high quality of patients suffering from vertigo-related illnesses were observed within the ENT clinic, which led to the formation of a research group on the topic.

Researchers at the Sapienza University Clinic of Rome, Policlinic Umberto I, have devoted particular attention to vestibular disorders, resulting in original contributions documented in more than 80 articles published in national and international journals in the second half of the twentieth century and the early years of the present century.

Undoubtedly, the most significant contribution recognized by the entire international community was the use of glycerol in Menière's disease. In 1964, an article by Italo De Vincentiis (Fig. 1) and colleagues (De Vincentiis et al, 1964) appeared in the journal Valsalva, founded in 1930 by Bilancioni. The article described the use of therapeutic glycerol in Menière's disease, with favorable and long-lasting hearing results in the first few weeks (Fig. 2).

Figure 1. Prof. Italo De Vincentiis

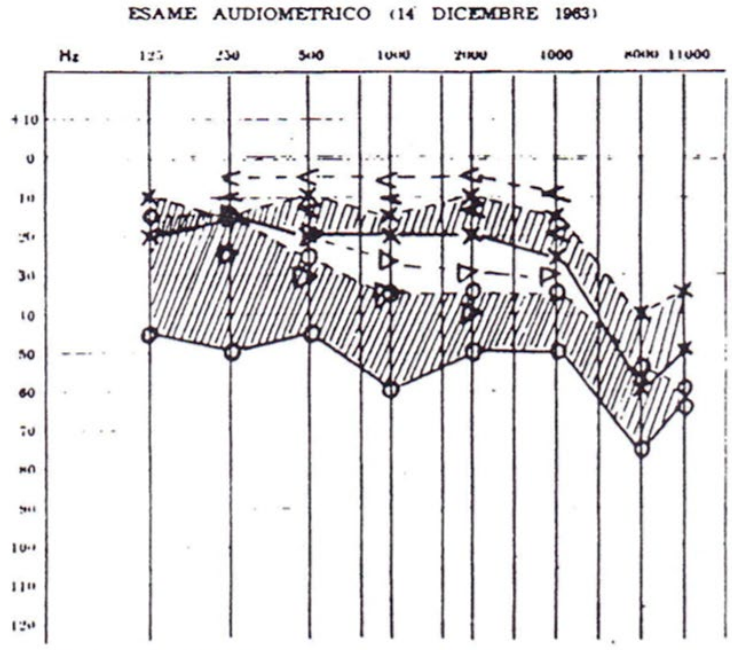

Illustration demonstrating hearing improvement following glycerol administration. (Reproduced from De Vincentiis *et al.*[2], by courtesy of the Editors of *Il Valsalva*.)

Figure 2. Original report of the first study demonstrating hearing improvement after glycerol administration.

Figure 3. Prof. Domenico Celestino

During those years at Policlinic Umberto I in Rome, glycerol was being used successfully in neurosurgery (Bovet, Cantore, Guidetti, cited in De Vincentiis et al., 1964) and ophthalmology (Virno, Cantore, Bietti, and Bucci, cited in De Vincentiis et al., 1964). The efficacy of oral administration in glaucoma had been observed. This evidence led Italo De Vincentiis (De Vincentiis et al., 1964) to experiment with the use of glycerol in Ménière's disease, which at that time was referred to as "labyrinthine glaucoma."

The article reported the experience gained on Menière's patients who had been administered glycerol orally. The almost immediate results were both subjective and objective,resulting in an improvement in hearing thresholds previously unheard of with other drugs.

The young Domenico Celestino (Fig.3) actively participated in the research group. In the fall of 1966, during a lecture at Uppsala University, he presented the Roman School's experience in an oral presentation: "...in 16 patients classified as having stage I Meniere's disease, with fluctuations in hearing thresholds and good cochlear reserve, the administration of glycerol was followed by a rapid, albeit transient, improvement in hearing, a reduction in tinnitus, and the disappearance of vertigo..." Furthermore, none of the other 30 patients in a more advanced stage of Meniere's disease or suffering from other vertigo syndromes had achieved significant improvements from the administration of glycerol..."

In the late 1960s, throughout the 1970s and early 1980s, Domenico Celestino's scientific activity was characterized by an important and meticulous collection of the clinical histories of the Menière's patients he saw.

Among other things, it is worth mentioning his commitment as founder of the National Working Group on Labyrinthopathies, whose primary goal was to develop a specific medical chart to facilitate large-scale and unambiguous data collection for Menière's patients. This chart was adopted by numerous hospital and university scholars from throughout Italy. Interesting insights come from studies on osmolality levels (Celestino & Ralli, 1981), "Plasmatic osmolality in Ménière's disease" (Journal of Laryngology and Otology, 95: 273–277).

Furthermore, his interest in the behavior of acid-base balance in Meniere's disease and other pathologies is well known. The latter was found to be altered with a tendency towards metabolic alkalosis exclusively in Ménière's patientswith hearing loss associated with recruitment. This phenomenon was interpreted as an evolutionary phase toward cochlear hydrops and considered a valid diagnostic aid for differentiation from other vestibular pathologies (Ralli et al., 1982).

Since then, the Roman clinic has conducted extensive research on Menière's disease, focusing on epidemiology, experimental and clinical pathophysiology, natural history, and medical and surgical treatments. Scientific interest has continued to this day, with numerous researchers taking up the mantle with publications both nationally and internationally.

In those years, on the basis of the collection of a significant number of cases, it was noted in Meniere's patients and on its seasonal recurrence, prevalent in spring and autumn. (Celestino et al, 1987).

Particularly significant are the findings of epidemiological studies on the incidence of Ménière's disease in Italy (Celestino & Ralli, 1991). At that time, published epidemiological studies showed widely conflicting results, reflecting a lack of diagnostic uniformity. Reported prevalence rates ranged from 3.5 per 100,000 to 513 per 100,000. The average annual number of new cases identified in this investigation was 8.5, corresponding to an incidence of 82.2 per 10^6 population. Disease prevalence was calculated by multiplying incidence by 25, yielding an estimated prevalence of 2,050 per 10^6. Extrapolated to a population of 57×10^6, this suggests approximately 16,850 cases of Ménière's disease in Italy. These data were later confirmed by Harris Alexander in a large population sample (90 million individuals) (Harris Alexander, 2010).

Subsequently, the impact of the initial symptoms on the evolution of the disease was studied, highlighting how the initial disorders of cochlear origin determined vertigo attacks of shorter duration (Ralli et al., 1995). It is worth highlighting the observations regarding recovery from the disease, understood not only as the absence of vertigo attacks, but also as the maintenance of normal, stable, and long-lasting hearing, identifying some significant parameters in an active disease period of less than 18 months and fewer than 39 vertigo attacks.

Numerous experimental pathophysiological studies have been associated with clinical research, especially regarding the effect of glycerol on endolymphatic hydrops. Giuseppe Magliulo, by surgically obliterating the sac and duct in an endolymphatic animal model, reproduced endolymphatic hydrops. The experimental hydrops allowed for a quantitative and qualitative evaluation of the effect of glycerol on this pathological condition using precise measurements of the endolymphatic area at different times after the onset of hydrops, with particular attention to the early stages. Guinea pigs treated with glycerol showed minimal dilation of the endolymphatic compartments or even absence of cochlear hydrops, confirming the therapeutic efficacy of glycerol (Magliulo et al., 1991a; 1991b). These findings were corroborated by electrophysiological studies with Mario Gagliardi, showing improved hearing thresholds measured by electrocochleography (Magliulo et al., 1992).

The introduction of new audiological and vestibular instrumental investigations in the late 1990s and early 2000s further stimulated clinical research.

The first area of interest concerned otoemissions was investigated by Giancarlo Cianfrone e Giovanni Ralli (Cianfrone et al, 2000). They studied distortion products be-

fore and after glycerol administration in a group of Meniere's patients. Fifty percent of the patients showed improvement, although this improvement was not correlated with an improvement in the threshold hearing threshold (). Giuseppe Magliulo and Giancarlo Cianfrone, in a group of patients suffering only from a sense of aural fullness in the absence of other associated symptoms or signs, and subjected to glycerol testing, observed a positive test in 58% of cases, confirming the importance of distortion products for their ability to identify subtle dysfunctions, potentially indicative of endolymphatic hydrops, that are missed by routine pure tone audiometric tests Magliulo et al 2001).

Studies on evoked vestibular potentials have been particularly rich in insights.

Giuseppe Magliulo and Mario Gagliardi, using a clinical model consisting of patients operated on for acoustic neuroma in which either the superior or inferior vestibular nerve was preserved, demonstrated in humans, and not in animal studies, the origin of C-Vemps in the saccular nerve and O-Vemps in the utricular nerve (Magliulo et al 2003, Magliulo et al 2008). Furthermore, they set up a research program to evaluate the ability of the glycerol test to identify endolymphatic hydrops in the phases by combining pure tone audiometry with distortion products and C-Vemps. This investigation allowed them to evaluate the impact of hydrops separately on the cochlear and vestibular compartments. The results showed some different test positivity for distortion products and vestibular potentials. In a group of patients, post-glycerol improvement involved only the Vemps, demonstrating in some patients the presence of hydrops that affected only the posterior labyrinth in the initial stages of the disease (Magliulo et al 2004a, Magliulo et al 2004b). These data confirmed the vision of Paparella, who already in the 1970s and 1980s hypothesized cochlear, vestibular, and cochleo-vestibular Meniere's disease.

Further research at our group has focused on the use of these new investigational methods in vestibular neuritis, studying all five vestibular receptors (saccule, utricle, superior, lateral, and posterior semicircular canals).

Concurrently, Giovanni Ralli (Ralli et al.) used C and O-Vemps in a group of patients with vestibular neuritis, identifying 50% of patients with superior vestibular nerve involvement and the remaining patients with superior vestibular nerve damage. The former showed no improvement in caloric tests, while the patients with inferior vestibular nerve involvement recovered both in caloric tests and vestibular reflexes.

Finally, Giuseppe Magliulo and Mario Gagliardi combined the use of vestibular potentials and vHIT in patients with vestibular neuritis. They were the first in the anglosaxon literature to report patients with vestibular neuritis with selective damage to the superior and lateral semicircular canals and related nerves, without any involvement of other vestibular receptors ().

Subsequently, they studied the evolution of recovery of the functionality of the 5 vestibular receptors at 6 months and 1 year from the onset of vestibular neuritis (Magliulo et al 2012a, magliulo et al 2014b, Magliulo et al 2015c).

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