Roid Rage: Historical Perspective on the Emergence of Oral Steroids as a Treatment of Idiopathic Sudden Sensorineural Hearing Loss

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Objectives: To review the historical circumstances that led to the emergence of corticosteroid therapy for idiopathic sudden sensorineural hearing loss (ISSNHL) and to discuss how this history has influenced current perspectives on the condition.

Methods: PubMed and Google scholar were used to identify articles of ISSNHL and oral corticoid steroid use. Historical articles accessed through our institutional medical library were also reviewed.

Results: The use oral corticosteroids as a treatment for ISSNHL was seemingly influenced by three key historical circumstances that, together, provided the substrate for the treatment's use in ISSNHL. First, ISSNHL was a frustrating condition with uncertainty regarding its etiology and few reliable treatment options. Second, the discovery of corticosteroids was awarded the Nobel Prize in 1950, which led to widespread application of this therapy. Third historical circumstance was the evolution and emergence of more rigorous methodological study designs in clinical research. In 1980, these events culminated in a double-blind study evaluating the effectiveness of oral steroids for treatment of ISSNHL. Interestingly, this study is often misrepresented as a randomized controlled trial, which ultimately contributed to adoption of a new standard for treatment in ISSNHL. Research subsequent to these historical events has challenged the notion of corticosteroids as a gold standard but has not altered the historically established paradigm of corticosteroid treatment.

Conclusions: The use of steroids as a treatment for ISSNHL evolved from our specialty's need to address a complex condition, a novel therapeutic discovery, and a landmark study that met emerging methodological standards. Despite these strong historical foundations, ISSNHL remains a condition with an unknown etiology and the therapeutic value of corticosteroids remains unpredictable despite their gold standard label.

Key Words: Corticosteroids—Idiopathic sudden sensorineural hearing loss—Randomized controlled trial—Viral neuropathy.

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INTRODUCTION

For any condition, it is important to understand the circumstances and thought processes that ultimately led to treatment paradigms. This is particularly true for complex conditions such as idiopathic sudden sensorineural hearing loss (ISSNHL). ISSNHL is a clinical disorder of unknown etiology defined by an acute reduction in sensorineural hearing over a 72-hour period (1). Despite being first described more than a century ago (2,3), ISSNHL is still poorly understood, and its pathophysiology remains elusive. Several theories about its mechanism emerged, including ischemic injury, inner-ear fluid imbalances, or viral insults (4–6). These original theories were described more than 50 years ago, and few advancements have been made since then to better elucidate our understanding of this disorder.

With the disorder's uncertain etiology and limited treatment options, ISSNHL has frustrated otologists and treating physicians who sought to understand the condition. In the early to mid-1900s, around the time the condition was documented in the medical literature, oral steroids were isolated and being used in the medical field to treat inflammatory conditions. As indications for corticosteroid use were growing, research methodology was evolving, and the importance of clinical study design was a consideration that affected the influence of research. These events ushered in the first double-blind study evaluating oral steroids in the treatment of ISSNHL (7).

Various nonsteroidal therapies were proposed for ISSNHL throughout these early decades, including histamines, vasodilators, anticoagulants, and procaine, among others (8). Of these, only oral corticosteroids have withstood the test of time. Interestingly, their efficacy as a therapy for ISSNHL is not as certain as the history suggests, and some analyses have suggested that corticosteroids may not be superior to placebo (9).

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In this article, we aim to provide a historical perspective on how oral corticosteroids became a standardized treatment option for ISSNHL. We propose that three key historical circumstances contributed to the widespread acceptance of this treatment paradigm: 1) the failure to confidently identify the causative etiology, 2) the discovery of corticosteroid therapies and eventual awarding of the Nobel Prize for their discovery, 3) and the evolution of clinical research methodology. We will discuss how history seemingly misrepresented a landmark study and how this history left a lasting effect on current treatment paradigms on ISSNHL.

METHODS

PubMed and Google Scholar were used to identify early publications on ISSNHL and oral corticosteroid use. Additional texts describing the emergence of oral corticosteroids and the development of the randomized controlled trial (RCT) in clinical medicine were identified with an online literature search. Any historical documents and archives related to this topic were reviewed from the History of Medicine section in our institutional library. Of note, our search was limited to articles, journals, and books written in English and did not include works written in other languages. As such, a comprehensive review of the earliest articles attempting to identify the etiology of ISSNHL may be beyond the scope of this present work.

HISTORICAL CIRCUMSTANCE 1: ATTEMPTS TO IDENTIFY THE ETIOLOGY OF ISSNHL

Sudden deafness was described as early as 1847, with multiple accounts recorded by Yearsley's (10) text, "Deafness practically illustrated: being an exposition of original views as to the causes and treatment of diseases of the ear." Although Yearsley's use of the term "sudden deafness" does not specifically distinguish between sensorineural hearing loss and conductive causes, it represents an early account of sudden changes in hearing as an otologic condition of importance. Within the English literature, one of the earliest accounts of sudden deafness related to a sensorineural condition was published in 1885, wherein two patients presented to the Glasgow Ear Hospital after having experienced sudden unilateral deafness (2). One of the patients was noted to have nausea, vomiting, and "severe giddiness" associated with the hearing loss. Without a formal audiogram to evaluate the degree of hearing loss, the authors describe that one of the patients could hear the tick of a watch 8 inches away in the normal hearing ear, but only 1 inch away in the affected ear. Despite treating these patients with a cholinergic agent, pilocarpine, the hearing could not be recovered. The authors concluded that "there can be little doubt that, in the two cases described here, the seat of the mischief was in the nervous apparatus of hearing."

In 1908, Ballenger (11) described in his textbook that "increased tension of the labyrinthine fluid produces deafness." He listed several potential causes of this "increased tension" and cites syphilis, tuberculosis, and "excessive administration of quinine" as possible causes. He wrote that the mechanism of the sudden deafness was "probably due to an anemia or a congestion of the labyrinthine membrane and auditory nerve endings."

With the advent of a clinical audiometer described in 1878 (12,13), clinicians gained the capacity to document sensorineural hearing loss (12). Kleyn (14) reported a series of 21 patients with ISSNHL in 1944 and described the disease entity with audiometric data, x-rays, and vestibular testing. Medical literature before Kleyn's study was limited to case reports. Since then, numerous theories emerged about the etiology of ISSNHL. The three most widely accepted theories have been an ischemic or vascular injury to the inner ear, cochlear fluid disruption or imbalances, and viral infection (15).

Some of the earliest histological studies lending support for a vascular injury model were described in the 1950s (16–20). Perlman et al. (21–25) systematically demonstrated through animal studies that disruption of the vascular supply to the inner ear produced devastating histopathologic changes to the cochlea and profound hearing loss. They established the foundation for other laboratory and clinical studies that supported the theory of microcirculatory compromise to the inner ear as the etiology of ISSNHL. With evidence supporting this theory, various therapies for ISSNHL aimed at improving blood flow to the inner ear were proposed such as calcium channel blockers (26); dextran (an anti-thrombotic agent) (27); vasodilator agents such as histamine, procaine, and nicotinic acid (28); and carbogen gas (95% O_2/5% CO_2), which could be inhaled by a patient (23,25).

Although these early studies initially supported a vascular insult theory to ISSNHL, other studies showed that many of these therapies were ineffective (29). In his article in 1984 entitled "Sudden Hearing Loss: Circulatory," Ugo Fisch wrote, "The title of this paper should end with a question mark. The experimental and clinical data on perilymph oxygenation accumulated in our department in the past 12 years indicate the presence of a circulatory disorder in sudden deafness. However, they do not permit one to decide whether this disturbance is primary or secondary in nature."

Around this time, another theory emerged proposing that ISSNHL was caused by cochlear membrane breaks with subsequent loss of the endocochlear potential (30). It is possible that this theory emerged because of the observation that some patients with ISSNHL were healthy without comorbid conditions that would predispose them to a vasculopathy. Some who were convinced of the validity of this theory suggested administering CT contrast dye (diatrizoate meglumine) intravenously for several days to treat ISSNHL with the idea that the dye had a similar molecular size and configuration as the "broken membrane pores," and the dye could fit into and plug these pores and restore the endocochlear potential (31). Without any solid evidence to support this theory, however, these treatments eventually fell out of favor for the treatment of ISSNHL.

The last major theory that became popularized around this time was the viral infection theory. One of the earliest accounts of a viral infection causing sudden deafness was in 1860, when Toynbee wrote that "the peculiar poison which

causes the disease generally known by the name of mumps is very often the source of complete deafness, which, however, usually occurs in one ear only" (32). In the mid-1900s, several reports proposed that ISSNHL was caused by a viral infection (33–35). This theory was further supported by histopathological studies, which suggested a possible direct viral infection from the meninges or via a hematogenous route (4,5). In addition to histopathological evidence, clinical observations and studies began drawing a link between viral infections and ISSNHL (36–38). Because antiviral medications, such as acyclovir, were experimental medications at the time and were not approved for medical use until 1980s, there were few therapeutic agents available to test the growing hypothesis that ISSNHL was virally mediated.

Ultimately, historical consensus has not been achieved as to the etiology of ISSNHL, and the present-day understanding of the condition remains unclear. This failure to achieve consensus is relevant because it undoubtedly influenced to the next historical circumstance that led to development of a potential ISSNHL treatment.

HISTORICAL CIRCUMSTANCE 2: DISCOVERY OF ORAL CORTICOSTEROIDS AS AN ANTI-INFLAMMATORY THERAPEUTIC AGENT

In the beginning of the 20th century, Addison's disease was still poorly understood and without a medical treatment (39). In 1930, however, a shift occurred in the treatment paradigm for Addison's disease. Investigators from Princeton University extracted a compound from cattle adrenal cortical tissue and successfully treated adrenal failure patients with this compound. Further extractions of compounds from animal adrenal cortex led to the isolation of 28 different adrenocortical steroids in 1939 (40).

Around this time, certain rheumatologic diseases such as rheumatoid arthritis (RA) that were originally considered to have an infectious etiology were beginning to be thought of as a "direct consequence of disturbance in the several functions of the neuro-endocrine system as a whole" (41). In 1949, cortisone was successfully used for the first time in the treatment of RA (42). In addition to the hormonal effects, the anti-inflammatory effects of steroids were also beginning to be recognized and reported (43). The authors in this study noticed that an RA patient "previously confined to a bed or wheelchair … became ambulatory" as the steroids effectively reduced the symptoms associated with an active RA flare. They also noticed that, with steroids, inflammatory markers such as "sedimentation rate (Westergren) in 1 hour decreased from 85 to 24 mm." After studying the effects of an array of steroids on RA patients, they concluded that steroids had four main effects: "antirheumatic, antipyretic, nutritional, and euphorigenic." Until that point in history, there had not been a single therapeutic agent that treated RA so effectively and what appeared to be with such specificity. Ultimately, Hench, Kendall, and Reichstein received the Nobel Prize in Medicine in 1950 for their discovery of cortisone and its application for the treatment of RA (44).

Given the widespread beneficial effects in RA, corticosteroids were applied to other inflammatory conditions such as eczema (45) and asthma (46). In the field of otolaryngology, steroids began to be used for otitis externa, nasal polyps, inferior turbinate hypertrophy, sinusitis, Bell's palsy, oral burns, and laryngitis (47). Naturally, they were also applied to ISSNHL, and one of the first reports on the use of steroids for the treatment of ISSNHL was published in 1957 by Flynn (47). Flynn wrote, "Certainly there is no place for the glucocorticoids in the treatment of deafness, even though they have been tried in cases of otosclerosis and other types." In 1974, Malik et al. (48) published a case series wherein no control group existed, and 10 patients with ISSNHL were treated with antihistamines and oral steroids. They reported that 40% of patients who received oral steroids recovered their hearing thresholds to normal levels. However, they acknowledged the limitations of their report by stating that "it is difficult to predict the results without any treatment because comparative studies have not been done, although cases with spontaneous recovery have been reported. Both the etiology and the ideal treatment of sudden hearing loss still remains a mystery." Thus, although case reports and case series of the use of corticosteroids in the treatment of ISSNHL were emerging, investigators acknowledged the need for a comparative study to determine whether the medication had true efficacy beyond what would be expected from spontaneous recovery.

Although this initial trial of steroids for ISSNHL had ambiguous results, important historical concepts had been developed. At this point in the 1970s, ISSNHL was solidified as a disorder without a clear etiology that was eager for therapeutic options. Next, corticosteroids had been awarded medicine's highest award and were being applied unsystematically to otolaryngologic disorders such as ISSNHL. This history ultimately led to the third necessary event to solidify corticosteroids as an established treatment paradigm: evolution of research methodologies to improve clinical study design. We will emphasize the historical role of study design by discussing the rise of the RCT, which quickly emerged as a gold standard in study design.

HISTORICAL CIRCUMSTANCE 3: EMERGENCE OF THE RCT IN CLINICAL MEDICINE

In the late 19th and early 20th centuries, improved understanding of disease pathology and introduction of novel treatments led investigators to develop more sophisticated methods to evaluate the efficacy of novel treatments in an unbiased way (49,50). Before the emergence of the RCT, "alternate allocation" trials were becoming more common in the medical literature starting in the 1890s when Johannes Fibiger (51) famously studied the efficacy of diphtheria antitoxin in 484 patients in Copenhagen. Alternate allocation trials were conducted by treating every other patient with an experimental therapy. Despite an improvement from case studies and expert opinion, however, alternate allocation trials still suffered from selection bias (52). In 1931, the research methodology evolved, and a study by Amberson et al. (53) introduced randomization in clinical trials. In this study,

investigators randomly determined which patients would receive sanocrysin for the treatment of tuberculosis with the use of a coin flip.

In 1948, concerned about ongoing issues of selection bias in allocation schemes, Austin Bradford Hill published the first RCT in the medical literature when he studied the efficacy of streptomycin in the treatment of tuberculosis by strictly concealing randomization of patients to control and treatment groups (54). The positive effect of strong methodological design was easily apparent, and RCTs quickly gained traction in the scientific community and became the gold standard by which pharmaceutical regulatory communities and clinical infrastructures determined the efficacy of a therapy.

CULMINATION OF HISTORICAL EVENTS: A DOUBLE-BLIND STUDY OF ORAL CORTICOSTEROIDS AS A TREATMENT FOR ISSNHL

Thus, the three circumstances discussed—the complex and uncertain etiology of ISSNHL, the discovery of oral corticosteroids and awarding of the Nobel Prize for its utility as a treatment of inflammatory conditions, and the emergence of improved research methodologies to evaluate a drug's efficacy—created the historical milieu for the first double-blind study in the field of otolaryngology in evaluating the efficacy of oral steroids as a treatment for ISSNHL (Fig. 1).

In 1980, Wilson et al. (7) published their research evaluating the efficacy of oral steroids in the treatment of ISSNHL. The study evaluated a total of 67 patients with ISSNHL within 10 days of hearing loss onset, 33 of whom received steroids, and 34 of whom received placebo. They also had 52 patients who did not wish to participate in the study and were included as another untreated group. The investigator and the patients were both blinded to the study drug, and it was thus conducted as a "double-blind" study. Follow-up audiograms were conducted at 1 month and 3 months after onset of hearing loss. The study found that patients with moderate hearing loss had a 78% chance of hearing recovery compared with 38% in controls. The authors concluded that "steroids have a definite positive effect on recovery." They also wrote, "we continue to conclude, therefore, that the most common cause of ISSHL is viral infection," based on the circumstantial evidence that many patients who had ISSNHL in their cohort had symptoms of upper respiratory illnesses.

Although this study presented definitive conclusions, with a methodology that was presumed to represent a "gold standard" approach, a closer review of this landmark paper a different result. First, despite being classified as an RCT by multiple subsequent studies (55,56), the Wilson et al. clinical trial did not use randomization to determine which patients received the study drug or placebo. Thus, the results of the study were subject to selection bias. Second, the study did not perform a formal power analysis to calculate the number of patients needed to minimize the risk of a type 1 error. Third, the steroid doses administered at the various institutions were different. Patients from one institution received a 12-day taper of 16 mg of prednisolone, whereas patients from the other institution received a 10-day taper of 4.5 mg of dexamethasone. Although these dosages were not equivalent based on known steroid potency data, the authors claimed that the "effect is thought to be roughly equivalent" (7). Fourth, the authors selectively withheld study drug from certain participants based on early study results, amplifying selection bias. They wrote, "the propensity for recovery in this group was recognized early in the study, and most were not included in the double-blind medication trial for fear that steroids would jeopardize their chance of recovery."

The study's conclusion that steroids have a "definite positive effect" on hearing recovery was overstated given the multiple issues with the study design. More importantly, the historical misrepresentation of this study as an RCT has produced a cascade of momentous support for this work under somewhat false pretenses. The study was presented under the auspices of an RCT, when in fact there is no discussion of randomization within this work. The word randomization does not appear within the article. History unassumingly bestowed the "RCT" designation on this work, and the downstream effect has been astounding. Despite its flaws, the influence of this study was immense, and the article has been cited more than 1,200 times to date.

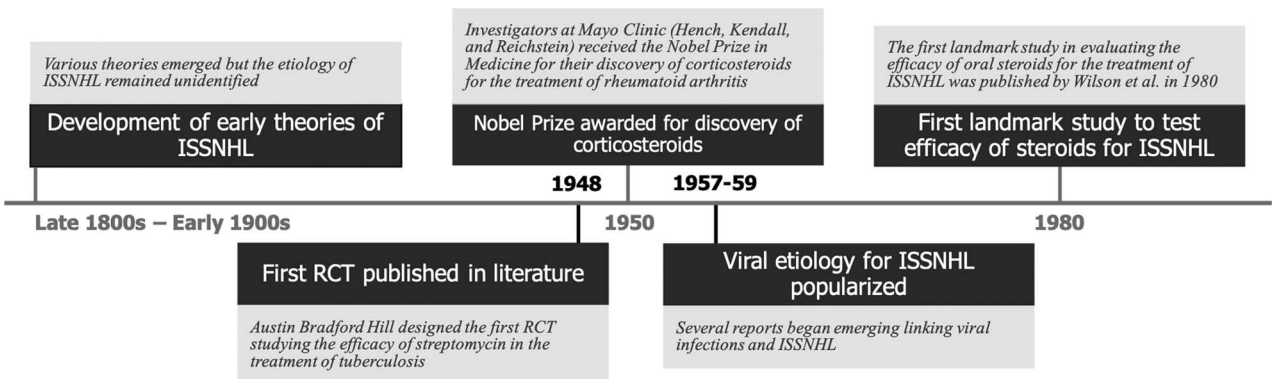

FIG. 1. Timeline of the key events leading up to the first landmark study performed by Wilson et al. (7) to evaluate the efficacy of oral corticosteroids in the treatment of ISSNHL.

HISTORY'S INFLUENCE

Four years after the Wilson et al. study was published, one of the original authors published a follow-up article as a Triological thesis summarizing 8 years of data on the treatment ISSNHL (57). In this article, the author wrote that "the treatment protocol reported here might have benefitted a few people in what Wilson and coworkers described as the 'steroid-effective zone' but did not have a demonstrable overall effect." The author concludes that "there is still no evidence that any treatment achieves a result better than expected from spontaneous recovery."

Since the study of Wilson et al., numerous studies were published to reproduce these results and establish the true efficacy of corticosteroids in the treatment of ISSNHL. A comprehensive review of all these studies is beyond the scope of this discussion. Nonetheless, two additional, formal RCTs were performed since then that did not demonstrate a significant benefit of oral steroids over placebo (58,59), and the largest systematic review and meta-analysis on this topic suggested no benefit to steroids (9,60). The American Academy of Otolaryngology–Head and Neck Surgery clinical practice guidelines of ISSNHL acknowledges that the efficacy of steroids in the treatment of ISSNHL is equivocal (61). The rationale behind offering this treatment option to patients is the "profound impact on quality of life" of ISSNHL and the "small possibility of hearing improvement" based on observational studies. Thus, despite the lack of clear evidence for the efficacy of oral steroids, it is the only treatment cited by the clinical practice guidelines from the American Academy of Otolaryngology–Head and Neck Surgery as a "reasonable treatment to offer to patients" (61).

The historical foundations of this therapy are complex and involve the introduction of Nobel Prize–winning drugs along with well-intended research methodologies to evaluate outcomes in ISSNHL. Despite the good intentions, historical overexuberance and misrepresented claims about a landmark RCT in 1980 complicated an already complex past. It is only through the lens of time that we have the insights to understand this perspective. In the present, we are often eager to promote progress, but if we do not know the history, we are bound to repeat it. Although steroids will, and probably should, remain a therapeutic option for ISSNHL, the insights we present are broadly relevant to the circumstances that lead to treatment paradigms. As future research develops novel therapies and approaches to challenging conditions, our specialty needs to ensure that circumstance does not cloud judgment and enthusiasm does not supersede evidence.

CONCLUSION

ISSNHL remains a complex condition to understand. Despite its equivocal efficacy, oral steroids continue to be recommended by otolaryngologists as a treatment of ISSNHL. The historical circumstances that led to steroids becoming a mainstay treatment option for ISSNHL were the challenges in identifying a specific etiology of ISSNHL, the discovery of steroids as a therapeutic agent, and the evolution and emergence of improve research methodologies, which led to a landmark study that had immense influence on the use of steroids for ISSNHL. As further research on ISSNHL helps us better understand the disease, our past experiences with establishing steroids as a mainstay treatment for ISSNHL will help us evaluate the efficacy of novel therapies in the future.

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