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Περιεχόμενα

Correction to Alexoudi (2024) in the article "Tissue biomarkers in Parkinson's disease and atypical parkinsonism" by Athanasia Alexoudi (Archives of Clinical Neurology, 2024, Special issue: Biomarkers in Parkinson's disease and atypical parkinsonism, Volume 33:2, March - April 2024, pp 38-67. https://www.jneurology.gr/ojs/index.php/aocn/issue/view/74/75), there was an error in the author affiliations and the Acknowledges section.

The author affiliations should be replaced by:
"Athanasia Alexoudi, MD, MSc, PhD,
1st Department of Neurosurgery, National & Kapodistrian University of Athens,
Neurological Institute of Athens."

"Αθανασία Αλεξούδη,
Α΄ Νευροχειρουργική Κλινική ΕΚΠΑ,
Νευρολογικό Ινστιτούτο Αθηνών."

The Acknowledgements section should be added, "Acknowledgements: This work is supported by the Alzheimer's Association ACSF-22-971298 fellowship grant to Dr. Athanasia Alexoudi."

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Dear colleagues,

As we embark on the beginning of summer, a season synonymous with growth and renewal, it is fitting to reflect on the dynamic landscape of neurological research. The longer days and brighter skies inspire a spirit of exploration and innovation. In this issue of Archives of Clinical Neurology, you may find 5 articles covering a wide spectrum of neurological entities.

First, in a narrative review of the existing literature performed by Papagiannopoulou et al., the current and novel therapeutic strategies in spinal muscular atrophy are presented. This rare genetic disorder may present with different clinical characteristics and variable prognosis in many stages of life, reflecting the need for familiarisation of the clinical neurologist both with the diagnosis and, more importantly, the treatment of the disease. Given the number of the existing disease modifying medications, it is critical that individualized therapies are offered to the appropriate patients.

Afterwards, Zambelis et al. present their interesting findings regarding the relative sensitivity of single fiber electromyography in orbicularis oculi and frontalis muscles in myasthenia gravis. Taking into consideration the high sensitivity of this diagnostic exam in neuromuscular transmission disorders, the authors recruited 51 myasthenia gravis patients and proved that both facial muscles show high sensitivity reaching 86.5% in the diagnosis of myasthenia gravis. This original article offers crucial insight in the diagnostic approach of myasthenia gravis.

Moreover, Koropouli et al. investigated whether continuous intestinal infusion of duodopa can ameliorate the motor and non-motor complications associated with advanced parkinson's disease. Given the high morbidity of this high prevalence disease, the administration of escalated treatment in the appropriate population proved to be beneficial and acceptably safe in the patients included in the study. This original article provides real world evidence for the safety of continuous intestinal infusion of duodopa in Greek patients with Parkinson's Disease.

Foska et al. present in the following publication 3 case reports with occipital neuralgia, who were treated with pulsed radiofrequency. Minimally invasive treatments have proven to be safe and effective when approaching patients with cephalalgia, especially taking into consideration the number of patients with resistance to conservative treatment. Foska and her colleagues showed that pulsed radiofrequency led to effective symptom control of the patients and suggested inclusion of patients in larger trials in order to prove the efficacy of this treatment. This case series provide timely information regarding the treatment of occipital neuralgia.

In the last article, Lima et al. provide a case report and a literature review regarding the relapse of recurrent painful opthalmoplegic neuropathy (RPON) after covid-19 vaccination in adult population. This article provides insight in the still unclassified pathophysiology of RPON supporting the hypothesis of neuropathy as the underlying cause of RPON, that causes the relapse following Covid-19 vaccination

In conclusion, as we stand at the threshold of summer, the neurological research field is brimming with promise and potential. The journey ahead is challenging, but the rewards are well worth the effort.

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ΝΩΤΙΑΙΑ ΜΥΪΚΗ ΑΤΡΟΦΙΑ: ΤΡΕΧΟΥΣΕΣ ΚΑΙ ΝΕΕΣ ΘΕΡΑΠΕΥΤΙΚΕΣ ΣΤΡΑΤΗΓΙΚΕΣ - ΑΝΑΣΚΟΠΗΣΗ.

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Περίληψη

Η νωτιαία μυϊκή ατροφία (SMA) είναι μια σπάνια γενετική διαταραχή που χαρακτηρίζεται από την προοδευτική εκφύλιση των κινητικών νευρώνων του νωτιαίου μυελού, οδηγώντας σε μυϊκή αδυναμία και ατροφία. Η πάθηση αυτή προκαλείται κυρίως από μεταλλάξεις στο γονίδιο του κινητικού νευρώνα επιβίωσης 1 (SMN1), το οποίο διαδραματίζει κρίσιμο ρόλο στη διατήρηση και τη λειτουργία των κινητικών νευρώνων. Η νόσος SMA εκδηλώνεται εντός ενός φάσματος κλινικών συμπτωμάτων και βαρύτητας, το οποίο σχετίζεται με την αντισταθμιστική λειτουργία της πρωτεΐνης SMN2, και ταξινομείται σε πέντε υποτύπους: τύπος 0 (συγγενής), τύπος I (νόσος Werdnig-Hoffmann), τύπος II (νόσος Dubowitz), τύπος III (νόσος Kugelberg-Welander) και τύπος IV (ενήλικη εμφάνιση). Μέχρι πρόσφατα, η θεραπεία ήταν μόνο συμπτωματική και περιλάμβανε αναπνευστική υποστήριξη, διατροφική υποστήριξη, φυσικοθεραπεία, ορθοπαιδική αντιμετώπιση των επιπλοκών. Ωστόσο, την τελευταία δεκαετία έχουν εγκριθεί και είναι πλέον διαθέσιμες αρκετές θεραπείες που τροποποιούν τη νόσο, όπως η ονασεμνογένη αμπεπαρβοβέκη, η νουσινερσένη και η ριζδιπλάμη. Σε αυτή την εποχή, κατά την οποία οι διαθέσιμες ειδικές για τη SMA θεραπευτικές επιλογές επεκτείνονται ενεργά, η αυξημένη κλινική υποψία και η άμεση και ακριβής διάγνωση της SMA (συμπεριλαμβανομένων των προγραμμάτων νεογνικού ελέγχου) είναι κρίσιμες για την έγκαιρη έναρξη εξατομικευμένης θεραπείας και την αλλαγή της πρόγνωσης των ασθενών με SMA.

Λέξεις Ευρετηρίου: Νωτιαία Μυϊκή Ατροφία, ονασεμνογένη αμπεπαρβοβέκη, γονιδιακή θεραπεία, αντινοηματικό ολιγονουκλεοτίδιο, νουσινερσένη, ριζδιπλάμη.

SPINAL MUSCULAR ATROPHY: CURRENT AND NOVEL THERAPEUTIC STRATEGIES – A NARRATIVE REVIEW.

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Abstract

Spinal Muscular Atrophy (SMA) is a rare genetic disorder characterized by the progressive degeneration of motor neurons in the spinal cord, leading to muscle weakness and atrophy. This condition is primarily caused by mutations in the survival motor neuron 1 (SMN1) gene, which plays a crucial role in the maintenance and function of motor neurons. SMA disease manifests itself within a spectrum of clinical severity, that is associated with the compensatory function of SMN2 protein, and is classified into five subtypes: type 0 (congenital), type I (Werdnig-Hoffmann disease), type II (Dubowitz disease), type III (Kugelberg-Welander disease), and type IV (adult-onset). Until recently, treatment was only symptomatic and included respiratory support, nutritional support, physiotherapy, orthopedic treatment of complications. However, during the

last decade, several disease modifying therapies have been approved and are now available, including onasemnogene abeparvovec, nusinersen, and risdiplam. In this era, when available SMA-specific treatment options are actively expanding, increased clinical suspicion and prompt and accurate diagnosis of SMA (including neonatal screening programs) are critical for the early initiation of individualized treatment and change in the prognosis of SMA patients.

Keywords: Spinal Muscular Atrophy, onasemnogene abeparvovec, gene therapy, antisense oligonucleotide, nusinersen, risdiplam.

Introduction

Spinal Muscular Atrophy (SMA) is a rare genetic disorder characterized by the progressive degeneration of motor neurons in the spinal cord, leading to muscle weakness and atrophy.[1] This condition is primarily caused by mutations in the survival motor neuron 1 (SMN1) gene, which plays a crucial role in the maintenance and function of motor neurons.[2] The loss of function or absence of SMN1 protein results in the impaired survival of motor neurons, leading to the characteristic symptoms of SMA. It is considered a rare disease (OMIMs: 253300, 253550, 253400, 271150) with an estimated incidence of approximately 1 in 10,000 to 20,000 live births, yet with a carrier frequency of 1/40 to 1/70 in the general population.[3] A recent nationwide study in Greece indicated an incidence of about 1/12,000, and a prevalence of at least 1.5/100,000.[4] SMA stands as one of the leading genetic causes of infant mortality (together with cystic fibrosis).[5]

SMA was first described by the Austrian neurologist Guido Werdnig, who presented two young brothers presenting "muscular dystrophy of neurogenic cause", that was later attributed to SMA type II.[6] Since then, it became apparent that the disease manifests itself within a spectrum of clinical severity that is associated with the compensatory function of SMN2 protein. Presently, SMA is classified into five subtypes: type 0, type I (Werdnig-Hoffmann disease), type II (Dubowitz disease), type III (Kugelberg-Welander disease), and type IV (Table 1). It is important to note that 25% of SMA cases involve adult patients, underscoring the need of familiarization of adult neurologists for the diagnosis and management of this disease.[7] Moreover, an organized and smooth transition from the pediatrician to the neurologist should also be considered.[8]

Until recently, treatment was only symptomatic and included respiratory support, nutritional support, physiotherapy, orthopaedic treatment of complications. However, several specific therapies have now been approved and are available (Figure 1).[9] Reflecting on over a century of research, this narrative review outlines the evolution of SMA research and treatment advancements, showcasing significant progress despite the ongoing quest for a cure.

Pathophysiology

The pathophysiology of SMA involves a cascade of events triggered by reduced levels of functional SMN protein.[10] Normally, SMN protein functions in various cellular processes, including the assembly of small nuclear ribonucleoproteins (snRNPs), which are essential for pre-mRNA splicing in the nucleus. In SMA, decreased levels of SMN protein compromise snRNP assembly, leading to aberrant splicing of mRNA transcripts, including those encoding crucial proteins for motor neuron survival and function. SMA may also be considered among the disorders of programmed cell death, caused by the inadequate control of apoptosis.[11]

In 95% of the cases, the genetic variation involves the complete deletion of the survival motor neuron 1 (SMN1) gene, located on the telomeric segment of chromosome 5q13.[12] A virtually identical gene known as SMN2, produces a comparable yet less biologically potent protein product.[13] While the human genome typically contains no more than two copies of SMN1, the number of SMN2 copies can vary. The protein produced by SMN2 seems to partially ameliorate the symptoms of SMA, with a greater number of SMN2 copies generally correlating with a less severe manifestation and progression of the disease.

The loss of functional motor neurons in SMA results in denervation of skeletal muscles, particularly in proximal muscles.[1] In addition to motor neuron degeneration, SMA pathophysiology involves secondary changes in the neuromuscular system and surrounding tissues. Muscle fibers undergo atrophy due to denervation, leading to muscle weakness and decreased muscle mass. Skeletal deformities, such as scoliosis and joint contractures, may develop as a result of muscle imbalance and weakness. Furthermore, respiratory muscles may become affected, contributing to respiratory insufficiency and an increased risk of respiratory infections, which are significant sources of morbidity and mortality in individuals with SMA.

Clinical Characteristics.

SMA type 0 is used to describe neonates with the disease, presenting with severe weakness and profound hypotonia, likely originating before birth, often accompanied by reduced fetal movements during pregnancy.[14, 15] The majority of these infants do not

achieve any motor milestones. Additional features include absence of reflexes, bilateral facial weakness, atrial septal defects, and joint contractures. Respiratory failure is a significant cause of both morbidity and mortality, necessitating immediate noninvasive ventilation or endotracheal intubation upon birth. Life expectancy is notably shortened, with the majority failing to survive beyond 6 months of age.[16] Furthermore, arthrogryposis multiplex congenita, characterized by congenital joint contractures affecting at least two regions of the body, has been observed. SMA type 0 is very rare and has been characterized (together with SMA type IV) as the outlier of the phenotypic spectrum of SMA.

SMA type I typically manifests within the first months of life.[17, 18] Characteristically, affected infants are incapable of maintaining a seated posture without external support. Clinical indicators include pronounced hypotonia, weak cry, and respiratory distress. These infants display an inability to lift their heads when positioned prone and exhibit substantial lag in head movement when being transitioned from a supine to seated position. Notably, their resting posture often assumes a distinct "frog-leg" stance, reflecting a state of muscular laxity ("floppy" baby).[19] Limb weakness manifests severely and predominantly proximally. Bulbar muscle weakness complicates feeding, leading to arduous ingestion, persistent gurgling, and predisposition to aspiration pneumonia. Notably, facial muscle weakness is comparatively mild, imparting an alert countenance to these infants. Extraocular muscles are not involved. Typically, muscle stretch reflexes are absent, while sensory examination yields normal findings. Fine, subtle involuntary finger movements, termed minipolymyoclonus, attributable to dense fasciculations, may be discernible.[20] Around 50% of affected infants exhibit tongue fasciculations. While contractures are uncommon in initial stages, they may develop subsequent to prolonged immobility. Fatality typically results from respiratory insufficiency, pneumonia, or malnutrition before the age of two.[21]

The onset of symptoms associated with ***SMA type II*** typically occurs between 6 and 18 months of age.[17] Developmental delays in motor milestones often serve as the initial indicators of neurological involvement, with noticeable weakness in the legs preceding weakness in the arms. A subtle hand tremor, attributed to minipolymyoclonus, may raise suspicion for the condition. While the distribution, pattern, and progression of weakness mirror those observed in SMA type I, the severity of type II is considerably less, and the disease advances at a slower pace. Most children with SMA type II eventually achieve the ability to roll over and sit without external support, although independent walking is rare. Weakness in the trunk muscles contributes to the development of a characteristic rounded kyphosis when seated, and as shoulder strength diminishes, mobility decreases, ultimately leading to confinement to a wheelchair. Over time, contractures affecting the hips and knees, clubfoot deformities, severe scoliosis, and hip dislocation may emerge (Figure 2). The long-term outcomes for individuals with SMA type II vary significantly; while some succumb to respiratory failure during childhood, many others survive well into their third or fourth decade of life.

The onset of ***SMA type III*** occurs after 18 months of age, typically between 5 and 15 years, and is characterized by difficulties in walking.[17] Patients who experience onset before age 3 are categorized as SMA type IIIa, while those with onset after age 3 are classified as SMA type IIIb. This condition often resembles limb-girdle muscular dystrophy. As weakness in the muscles around the hips and pelvis progresses, affected individuals may exhibit a waddling (Trendelenburg) gait, accompanied by a protruding abdomen due to increased curvature of the lower spine, making climbing stairs challenging. To rise from a supine position on the floor, individuals may employ the Gowers maneuver. Subsequently, atrophy and weakness in the neck, shoulders, and arms develop, although lower extremity weakness typically surpasses that of the upper extremities. Fasciculations are more pronounced compared to SMA types I and II, and a fine tremor during movement is frequently observed. Tendon reflexes consistently diminish and eventually disappear, while sensory examination yields normal findings. The clinical course of SMA type III is characterized by a slow progression, often punctuated by prolonged periods of stability lasting several years. Predicting the eventual level of disability is challenging; however, if symptoms onset after age 2, it is probable that the individual will maintain ambulatory function well into their fifth decade of life and enjoy a lifespan comparable to that of the general population.

The majority of cases of the autosomal recessive, 5q-associated adult-onset, ***SMA type IV*** predominantly affect the proximal muscles.[22] Clinically, these cases present with a gradually progressive weakness in a limb-girdle fashion, resulting in challenges with walking, climbing stairs, and standing from a seated or prone position. Fasciculations are a notable finding, observed in approximately 75% of patients, with pronounced weakness often evident in the quadriceps muscles. While muscle cramps may occur, they are not a prominent feature, and bulbar signs, bony deformities such as scoliosis, and respiratory weakness are infrequent. The distribution of weakness in many cases resembles that seen in limb-girdle muscular dystrophies, hence the historical term "pseudomyopathic SMA".[23] Similarly to the recessive form, the majority of the cases of the autosomal dominant

adult-onset SMA, also known as Finkel-type SMA, typically commence in the third decade of life, predominantly affect proximal muscles, progress very slowly, and initially involve the legs before affecting the arms.[24] The majority of patients retain ambulatory function for decades following symptom onset.

Diagnosis.

SMA diagnosis involves a combination of clinical evaluation, genetic testing, electrophysiologic studies (electroneurography and electromyography) and, very rarely, muscle biopsy.

Clinical suspicion often arises from characteristic signs and symptoms observed during infancy or childhood, including progressive muscle weakness, hypotonia, decreased motor function, and respiratory difficulties.

Genetic testing is the cornerstone of SMA diagnosis, particularly identifying variations or deletions in the SMN1 gene on chromosome 5q13.[25] The absence or variation of SMN1 gene copies confirms the diagnosis, as nearly all SMA cases result from alterations in this gene. Additionally, the number of copies of the SMN2 gene, a closely related homolog of SMN1, may be evaluated. While SMN2 cannot fully compensate for the loss of SMN1, a higher number of copies may correlate with milder phenotypes due to increased production of functional SMN protein.

Electrophysiologic studies can provide supportive evidence for SMA diagnosis by assessing motor nerve function and detecting abnormal electrical activity in affected regions.[26] Compound muscle action potentials may exhibit diminished amplitudes, yet conduction velocities and sensory nerve conduction studies typically remain within normal ranges. During needle electrode examination, signs of acute denervation, such as fibrillation potentials and positive sharp waves, alongside fasciculation potentials, may be observed, indicating ongoing motor nerve damage. Additionally, evidence of chronic motor unit remodeling, stemming from a prolonged cycle of denervation and reinnervation, may manifest.

With the advent of genetic testing, muscle biopsy is less frequently utilized for SMA diagnosis.[27] It is typically reserved for situations where genetic testing results are inconclusive or unavailable. It may also be considered when there is a need to differentiate SMA from other neuromuscular disorders with similar clinical presentations. Muscle biopsy findings often reveal a distinct pattern known as grouped fascicular atrophy, particularly prominent in classic Werdnig-Hoffmann presentations. This pattern entails the atrophy of entire fascicles or groups of fascicles, juxtaposed with neighboring fascicles, often comprising hypertrophic fibers, predominantly of type I. However, it is crucial to note that myopathic alterations, such as variability in fiber size, fiber splitting, presence of internal nuclei, and fibrosis, may complicate the histological presentation, particularly in long-standing denervating disorders like childhood and juvenile SMA.

Management.

4a. Supportive Management

Current specific treatments for SMA do not provide a cure but instead aim to halt the disease progression. Therefore, supportive management remains the cornerstone of treatment. Supportive management of SMA aims to address the symptoms and complications associated with the condition, improve quality of life, and optimize functional abilities. A coordinated and multidisciplinary approach, typically involving neurologists, pulmonologists, physical therapists, occupational therapists, speech therapists, nutritionists, and social workers, is essential to offer SMA patients comprehensive care.

Given the respiratory complications associated with SMA, respiratory support is crucial.[28] This may involve interventions such as non-invasive ventilation, cough assistance devices, and airway clearance techniques to help maintain lung function, prevent respiratory infections, and manage respiratory distress. Orthopedic management plays a crucial role in the care of SMA patients, as contractures and scoliosis are notable comorbidities.[29] Orthopedic surgeons are involved in recommending interventions such as spinal fusion or the placement of spinal growing rods, particularly in cases of severe scoliosis that impairs respiratory function though restrictive lung disease. Additionally, physical therapy plays a vital role in maintaining range of motion, preventing contractures, and preserving functional mobility.[30] Therapeutic exercises tailored to the individual's needs can help strengthen muscles, improve posture, and enhance overall physical function. Furthermore, occupational therapy may facilitate activities of daily living, promote independence, and maximize participation in meaningful activities, including (but not limited to) the use of assistive devices, adaptive seating, and ergonomic modifications to optimize comfort and functionality. Importantly, speech therapists can address speech and swallowing difficulties commonly observed in individuals with SMA, providing interventions to improve oral motor function, swallowing safety, and communication skills. They may also assist with dietary modifications and feeding techniques to ensure adequate nutrition and hydration, together with the nutritionists that assess nutritional status, provide dietary counseling, and recommend nutritional supplements or feeding tubes as needed to address feeding difficulties and prevent malnutrition. Coping with a chronic condition like SMA can be emotionally challenging for both

individuals and their families. Psychosocial support services, including counseling, support groups, and access to community resources, can provide emotional support, education, and guidance to help navigate the psychosocial aspects of living with SMA.[31] Finally, palliative care focuses on improving quality of life and relieving symptoms associated with serious illnesses, including SMA.[32] Palliative care specialists can help manage pain, alleviate discomfort, and address end-of-life care preferences in a compassionate and holistic manner.

In addition to supportive care, significant advancements have been made in the treatment of SMA. Novel treatments such as gene therapy, antisense oligonucleotide therapy, and small molecule drugs have revolutionized the management of SMA by targeting the underlying genetic cause of the disease (Table 2).

4b. Gene Therapy

Onasemnogene abeparvovec, marketed as Zolgensma, was granted approval by the US Food and Drug Administration in May 2019 as a gene therapy for treating SMA in children under the age of two and by and the European Medicine Agency in June 2020 for all patients with a biallelic mutation in SMN1 and a clinical diagnosis of spinal muscular atrophy type 1 or up to three SMN2 copies. It comprises a single-dose, intravenous infusion of a non-replicating adeno-associated virus vector 9 (AAV9) capable of crossing the blood-brain barrier and carrying a functional copy of the SMN1 gene.[33] The AAV9 vector does not integrate into host DNA. Once inside the host cell, the AAV9 vector migrates to the nucleus, where the transgene functions as an episome – a distinct, stable chromosome apart from the host's native chromosome. Nevertheless, AAV vectors carrying single-stranded DNA exhibit limited gene expression efficiency since double-stranded DNA synthesis is necessary before gene expression can occur.

Initially, the phase 1 START trial evaluated the safety and efficacy of a single intravenous infusion of onasemnogene abeparvovec in symptomatic infants under 8 months of age diagnosed with SMA type 1 and possessing two copies of SMN2. Fifteen infants were enrolled, receiving either a low dose (6.7 ×10^13 viral genomes (vg)/kg; n = 3) or a high dose (1.1 ×10^14 vg/kg; n = 12) of intravenous onasemnogene abeparvovec.[33] At 20 months of age, all 15 infants were alive and did not require mechanical ventilation, marking a significant improvement compared to the 8% survival rate observed in historical control groups. Thirteen patients from the START trial participated in a long-term follow-up study, where all 10 children from the high-dose cohort remained alive without requiring permanent ventilation and maintained previously achieved motor milestones for up to 7.5 years post-treatment, underscoring the enduring efficacy of onasemnogene abeparvovec.[34]

The subsequent phase 3 trials, STR1VE-US and STR1VE-EU, administered the high dose utilized in the START trial to children under 6 months old diagnosed with SMA type I and possessing up to two copies of SMN2.[35, 36] Both trials revealed that over 90% of infants survived without requiring permanent ventilation at 14 months, compared to only 26% in the natural history cohort; moreover, approximately half achieved independent sitting by 18 months, a milestone not reached in the natural history cohort. Both STR1VE trials demonstrated a highly favorable benefit–risk profile for intravenous administration of onasemnogene abeparvovec in symptomatic infants with SMA under 6 months old, thereby bolstering the case for drug approval. This advantageous benefit–risk profile was further corroborated by the SPR1NT trial, which treated pre-symptomatic infants under 6 weeks old with 2 (n = 14) or 3 (n = 15) copies of SMN2.[37] While the START, STR1VE, and SPR1NT trials assessed the safety of onasemnogene abeparvovec in both symptomatic and pre-symptomatic infants with SMA, all participants weighed less than 8.5 kg. The industry behind onasemnogene abeparvovec initiated the Global Managed Access Program (GMAP) in January 2020, offering treatment to all SMA patients under 24 months old and weighing up to 21 kg. GMAP data indicated that safety outcomes for patients weighing 8.5 kg or more at the time of infusion were consistent with prior data from patients weighing less than 8.5 kg.[38]

Conclusively, during those clinical trials, onasemnogene abeparvovec demonstrated significant improvements in event-free survival, motor function, and attainment of motor milestones in SMA patients, with these benefits sustained over the long term (up to approximately 5 years).[34] Importantly, onasemnogene abeparvovec was also associated with an accelerated attainment of age-appropriate motor milestones and enhanced motor function in pre-symptomatic SMA children,[37] underscoring the advantages of early intervention and potentially the need for newborn screening programs. A recent systematic review and meta-analysis of all available studies confirmed that administration of onasemnogene abeparvovec was associated with better clinical outcomes, a finding that was more enhanced among the presymptomatic participants.[39] Importantly, this treatment exhibits favorable tolerability overall, notwithstanding the recognized risk of hepatotoxicity, which can typically be managed with prophylactic prednisolone. Recent real-world data derived from the RESTORE registry have also confirmed effectiveness of onasemnogene abeparvovec over a large patient population (168 patients), while demonstrated a safety profile consisted to that noted in the clinical trials.[40]

Although treated young patients have shown remarkable outcomes, the greater viral dosage required for older children and adults raises valid safety apprehensions. Indeed, there have been reports indicating that heavier children who received larger doses of onasemnogene abeparvovec presented more often elevated liver transaminase levels,[41, 42] although not consistently.[38] Exploring intrathecal administration of onasemnogene abeparvovec aims to address the challenge of requiring exceptionally high vector genome copies for intravenous treatment in older, and consequently heavier, patients. This approach seeks to achieve more effective transduction of the central nervous system.[43] A recent clinical trial explored the utilization of onasemnogene abeparvovec in older children via a fixed dosage and intrathecal administration, showing encouraging results.[44] A phase III trial, the STEER trial is currently recruiting, aiming to enroll 125 SMA patients aged ≥2 to <18 years old regardless of their weight, that will be treated with intrathecal administration of a fixed dose of onasemnogene abeparvovec. Study completion is expected in early 2025.

In addition to the constrained indications, primarily focused on young SMA patients, another obstacle of the gene therapy with onasemnogene abeparvovec is its limited accessibility and affordability, particularly in middle- and low-income countries.[45, 46] While a price of ≈ €1.7 million per dose sounds exorbitantly high in the public domain, the cost-effectiveness of onasemnogene abeparvovec, being a single-time treatment limited to new ("incident") cases, has been proven in various settings.[47-49]

Finally, regarding combined treatment, real-world data support the use of "add-on therapy" of nusinersen or risdiplam on top of onasemnogene abeparvovec (that has been previously administered) or the "bridging therapy", during which patients that were already treated with nusinersen or risdiplam receive onasemnogene abeparvovec.[40, 50-53] Currently, there is one ongoing, phase 4 trial, the RESPOND study evaluating the safety and efficacy of nusinersen in 60 patients (young children; aged 2 to 36 months) following treatment with onasemnogene abeparvovec. This trial is estimated to be completed at the end of 2025. Additionally, the JEWELFISH trial, testing risdiplam, enrolled patients that have previously received another disease modifying treatment, including onasemnogene abeparvovec (14 patients).[54] For the time being, there has been no there are no consensus guidelines on treatment choices, switching of treatments, or the indications of combination therapy.[55]

4c. Nusinersen

Nusinersen, classified as an antisense oligonucleotide, is administered intrathecally into the cerebrospinal fluid. It targets a specific region within intron 7 of the SMA gene, known as ISS-N1,[56] modulating the splicing of the SMN2 pre-mRNA, thus augmenting the expression of functional SMN protein.[57] Nusinersen is the first disease-modifying treatment that was approved in US in 2016 and in Europe in 2017.

Despite approval by the regulatory authorities for treating all SMA forms (including adults with SMA), initial clinical trials were confined to patients up to 14 years old, diagnosed with SMA types 1, 2, and 3, who were not reliant on mechanical ventilation. The first trial, known as the ENDEAR trial, was a phase 3 study focusing on the efficacy and safety of nusinersen in infants diagnosed with spinal muscular atrophy (SMA) types I and II.[58] This trial employed a randomized, double-blind, sham-controlled design and involved 122 infants. Among them, two-thirds received nusinersen treatment, while the remaining underwent sham treatment, with the final assessment conducted 394 days post-intervention. The sham arm was terminated prematurely during an interim analysis due to a significant disparity in survival rates between the two groups. In the final analysis, a considerably higher proportion of infants treated with nusinersen achieved a motor milestone response compared to those in the control group (51% versus 0%, respectively). Additionally, the event-free survival rate was significantly greater in the nusinersen group than in the control group (HR: 0.53, p=0.005), and overall survival was also notably higher among nusinersen-treated patients compared to the control group (HR: 0.37, p=0.004). Furthermore, patients with a shorter disease duration at screening were observed to be more likely to benefit from nusinersen treatment compared to those with a longer disease duration, highlighting the need for prompt diagnosis, potentially employing newborn screening programs.[59]

A similar study design was employed by the CHERISH trial, that included 126 children (2-12years old) with SMA types II and III.[60] This study was prematurely terminated due to favorable outcomes noted during the interim analysis in the interventional arm. In the nusinersen group, patients showed a notable increase of 4.0 points in the 15-month Hammersmith Functional Motor Scale Expanded (HFMSE) score compared to baseline, whereas those in the control group experienced a decrease of 1.9 points (p<0.001).

The EMBRACE study also used a similar design (phase 2, randomized, double-blind, sham-procedure controlled study) and included 21 patients that would have been considered ineligible by the two previous trials.[61] The part 1 of this study was terminated prematurely, following the observed motor function improvements associated with nusinersen in the ENDEAR trial, allowing the enrolled patients to roll over to an open label extension study of nusinersen,

the SHINE trial. Despite its early termination and the limited sample size, the EMBRACE study managed to demonstrate a favorable long-term benefit-risk profile in this broader population of SMA patients.[61]

Since then, the inclusion of a sham comparator in nusinersen clinical trials was considered rather unethical. Thus, the NURTURE trial was designed as an open-label, single-arm study aimed at administering nusinersen to 25 presymptomatic infants possessing two or three copies of SMN2 gene within the first six weeks of life.[62] During the three-year follow-up, no instances of death or the necessity for continuous assisted ventilation were reported. Concerning motor milestones, all patients achieved the milestone of sitting without support, with 92% of them walking with assistance, and 88% walking independently. An additional two-year follow-up was also available, confirming the durability of treatment effect.[63] These findings underscore the critical importance of promptly initiating proactive nusinersen treatment following a genetic diagnosis of SMA in presymptomatic infants.

Not only the efficacy, but also the effectiveness of nusinersen has been largely confirmed by a rising number of real-world studies, concerning adult patients as well.[64-67] One of the largest observational studies was conducted in Germany and showed clinically meaningful improvements in motor function among a total of 139 adult SMA patients (aged 16-65 years).[68] Feasibility was also proven by a number of them, especially concerning the lumbar puncture, which can be challenging among patients with severe scoliosis or corrective spondylodesis.[69, 70] To address potential difficulties in managing the intrathecal administration of nusinersen, several approaches have been proposed: fluoroscopy-guided, CT-guided,[69, 71, 72] ultrasound-guided,[73] lumbar laminotomy,[74] transforaminal approach versus the conventional interlaminar approach,[75, 76] cervical versus lumbar approach.[77] A recent systematic review and meta-analysis collected all available 12 cohort studies and case-series and summarized the cumulative data of 384 adult SMA patients treated with nusinersen.[78] According to the data analysis, a statistically significant improvement on motor function, as assessed by the Hammersmith Functional Motor Scale Expanded and the Revised Upper Limb Module scores, was shown, while adverse events were limited to the administration procedure (namely, post lumber puncture headache and back pain).[78] More rare adverse events have been also reported, such as coagulation abnormalities and thrombocytopenia (including acute severe thrombocytopenia)[79] and renal toxicities (including fatal glomerulonephritis),[80] while the development of antidrug antibodies is infrequent with unknown clinical significance.[80]

A significant aspect to contemplate when it comes to nusinersen treatment is its substantial expense and the procedures involved in reimbursement:[81] a single dose of nusinersen is estimated to cost €72,000, resulting in a total expenditure of €430,000 for the initial year of treatment, followed by €220,000 annually thereafter. Yet, the significant financial strain associated with the symptomatic treatment and the disease course SMA patients underscores the high cost-effectiveness ratio of nusinersen treatment at the present price.[82] Another important consideration is that the clinical trials had a restricted duration of follow-up, offering limited understanding regarding the long-term consequences of nusinersen therapy.[83] A potential challenge that could complicate clinical practice is determining when the potential risks of continuing therapy for a specific patient outweigh the ongoing benefits, raising the issue of treatment discontinuation.[84, 85] Despite the consistent demonstration of efficacy in both clinical trials and real-world settings, there remains a need for further investigation into the long-term effects of nusinersen.

4d. Risdiplam.

Risdiplam is another option that has recently been added in the therapeutic arsenal for SMA. Its notable advantage lies in the sufficient distribution through oral administration, both in the central nervous system and in the periphery. Risdiplam is a small-molecule compound that targets two regions (TSL2 and ESE2) on exon 7 of the SMN2 gene and modulates SMN2 pre-mRNA splicing within the nucleus,[86] leading to increased levels of functional SMN protein. Risdiplam was granted approval in the US in 2020 and in Europe in 2021, initially for patients with SMA older than 2 months, subsequently expanding to all age groups. It is administered once daily, with the dosage adjusted based on the patient's age and body weight. For adults and children over 2 years old weighing 20 kg or more, the recommended dose is 5 mg per day. For children older than 2 years old but weighing less than 20 kg, the recommended dose is 0.25 mg/kg per day. For younger infants, the recommended dose ranges between 0.15-0.2 mg/kg once daily.

The efficacy of Risdiplam has been assessed in four pivotal trials. The FIREFISH trial (Part 1) constituted a phase 2-3, open-label study that enrolled 21 infants with SMA type I, aged 1-7 months old, and randomized them into two groups: the "low-dose" group receiving a dosage of 0.08 mg/kg per day and the "high-dose" group receiving 0.2 mg/kg per day.[87] Both groups showed an increase in the median concentration of SMN protein. Notably, seven infants in the high-dose group achieved the milestone of sitting without support for at least 5 seconds, while none in the low-dose group reached this milestone. Consequently, the higher dosage of

risdiplam (0.2 mg/kg per day) was selected for the subsequent phase of the study: the FIREFISH trial (Part 2). In this trial, 41 infants were included and treated with risdiplam 0.2mg/kg daily, and 29% of them achieved the milestone of sitting without support for at least 5 seconds at the 12-month follow-up, additionally showing significant improvements in motor function compared to historical controls.[88] After 24 months of treatment, 44% of infants were able to sit without support for at least 30 seconds, though they were still unable to stand unassisted.[89]

The SUNFISH trial enrolled patients with SMA type II and type III, aged between 2-25 years. The Part 1 of the study was a placebo-controlled, dose-finding study, aiming to identify the most appropriate dose, based on safety, tolerability, pharmacokinetic, and pharmacodynamic data among the 51 included patients.[90] According to the findings of Part 1, the selected dose for Part 2 was 5 mg for patients weighing ≥20 kg or 0.25 mg/kg for those weighing <20 kg. Part 2 was a phase 3, double-blind, placebo-controlled study with international recruitment, including 180 SMA patients that were randomized to receive either risdiplam or placebo for 12 months.[91] This study showed significant improvement in motor function among patients treated with risdiplam compared to placebo, while serious adverse events were similar between the two groups. Following the 12-month follow-up, all included patients were offered risdiplam administration for an additional year.[92] This extension of SUNFISH Part 2 trial confirmed the favorable efficacy and safety profile of risdiplam at this longer follow-up.

The JEWELFISH trial, which is a multicenter, exploratory, non-comparative, open-label study, enrolled 174 patients with SMA type I, II and III, aged between 6 months and 60 years, that had previously received another disease modifying treatment (RG7800, olesoxime, nusinersen, or onasemnogene abeparvovec). In the interim analysis of this study, that was conducted after 1 year of treatment with risdiplam, it was shown that safety and pharmacodynamics (including the increase of SMN protein) were consistent in patients who had received any previous treatment compared to those that were treatment naïve.[54] The results of the primary analysis at 24-month follow-up have been announced at the Muscular Dystrophy Association Clinical and Scientific Conference 2023, showing a sustained >2-fold increase in median SMN protein levels versus baseline, irrespective of previous treatment and stabilization of the overall motor function,[93] while the peer-reviewed publication is awaited.

Finally, the single-arm RAINBOWFISH trial is currently ongoing and enrolling presymptomatic infants (aged from birth to 6 weeks old) with SMA and two or three SMN2 copies. Preliminary data of this trial have recently been released, showing that the motor scores of the 5 patients receiving risdiplam for at least 12 months were similar to those of young children without spinal muscular atrophy.[94]

Growing evidence from real-world data supports the safety and effectiveness of risdiplam.[95-98] This data highlights its positive impact on both measurable motor function outcomes and patient-reported reported outcomes.[99, 100] Furthermore, it indicates risdiplam as a viable option for individuals ineligible for gene therapy or those unable to tolerate or who have failed nusinersen treatment.[101] Switching from nusinersen to risdiplam has recently been demonstrated as feasible and safe, while motor improvements remained among the 17 adults included in this observational study.[102]

4e. Further considerations.

Despite the huge advancements in the treatment of SMA, several clinical unanswered questions remain. Exploring the optimal dosages of onasemnogene abeparvovec, nusinersen, and risdiplam beyond the parameters investigated in current clinical trials is crucial. Additionally, determining the ideal therapeutic window and evaluating the potential for switching or combining survival motor neuron protein-enhancing therapies, along with adjunct therapies independent of survival motor neuron protein, is essential.

Consideration should be given to prenatal intervention in fetuses with one or even two SMN2 copies, weighing the safety and efficacy of in utero treatment versus early delivery followed by prematurity treatment. Similarly, assessing the benefits of treating presymptomatic infants with four or more SMN2 copies is vital. Pediatric neurologists should familiarize themselves with newborn screening protocols to enable early detection and prompt intervention for infants diagnosed with spinal muscular atrophy. Additionally, they should remain vigilant regarding potential delayed systemic adverse events, as well as monitor for drug-related toxicities.

Understanding the unique adverse events associated with these emerging therapies over extended treatment periods is necessary for informed decision-making. Furthermore, anticipating changes in disease characteristics with aging and implementing appropriate surveillance measures is important. Neurologists are expected to encounter adults with severe spinal muscular atrophy who, with treatment, are increasingly likely to survive into adulthood. They also need to be prepared to manage adults for whom the benefits of treatment may be subject to debate, as some argue that the modest benefits do not justify the significant costs to both the individual and society. Identifying the most effective clinical biomarkers or patient-reported outcome measures for monitoring disease progression and treatment response,

particularly in adults, is critical.

Finally, establishing centralized international real-world longitudinal databases is imperative for monitoring the long-term efficacy, durability, and potential toxicities of available treatments, as well as for identifying treatment responders and non-responders, and documenting treatment-induced changes in disease presentation. Expert consensus is essential for determining surveillance protocols aimed at detecting organ involvement that may not manifest clinically but could render individuals more susceptible to environmental or other stressors.

Conclusions.

Recent advancements in treating SMA represent a significant transition from merely addressing symptoms to targeted therapies, showcasing notable progress in research. The gene therapy onasemnogene abeparvovec, recently approved for SMA treatment, has demonstrated substantial improvement in both survival rates and motor function during clinical trials. Nonetheless, challenges such as limited accessibility, affordability, and safety concerns among older patients persist, prompting ongoing investigations into combination therapies with nusinersen or risdiplam. Nusinersen, the pioneer disease-modifying treatment for SMA, has been approved for use across diverse age groups, based on both clinical-trial and real-world data. Risdiplam, a newly sanctioned SMA treatment, boasts oral administration convenience and has exhibited efficacy across various age groups, making it a feasible alternative for individuals ineligible for gene therapy or intolerant to nusinersen. Exploring optimal dosages, therapeutic windows, and the benefits of prenatal intervention and presymptomatic treatment, along with incorporating newborn screening protocols, are pivotal endeavors. Establishing centralized databases and formulating consensus guidelines are vital for ensuring long-term treatment monitoring and enhancing patient care in SMA.

Disclosures

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Figure 1. Launch dates of targeted therapies for Spinal Muscular Atrophy in Europe and in the United States of America (USA).

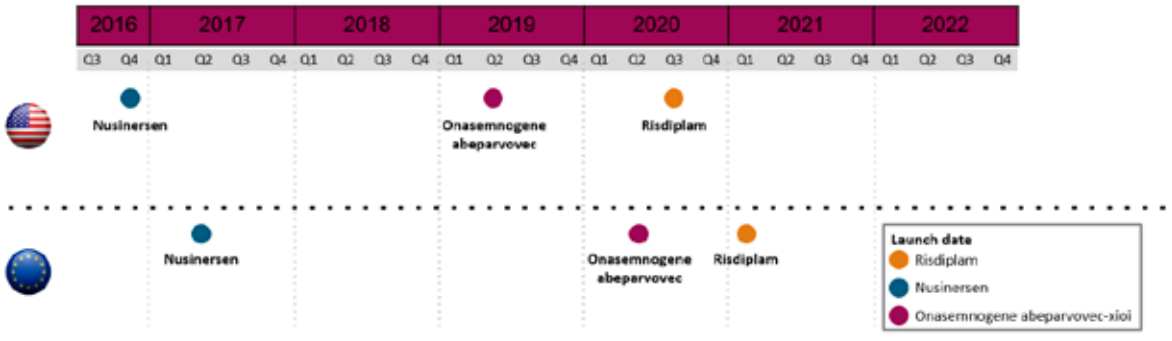

Figure 2. Severe scoliosis in an adult patient with Spinal Muscular Atrophy type II (A). The patient has been treated with computed-tomography-guided transforaminal intrathecal nusinersen injections (B) without any complications and excellent adherence for the past 4 years.

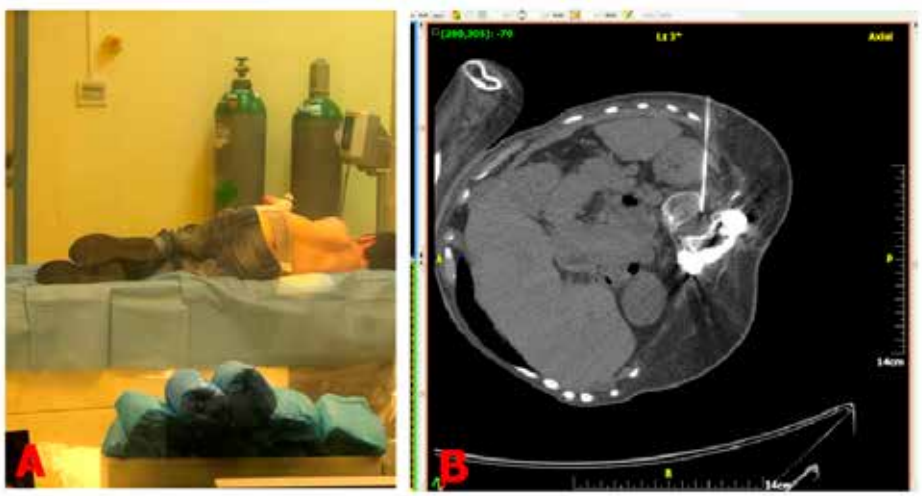

Table 1. Classification of Spinal Muscular Atrophy.

Type	Age of symptoms occurrence	Clinical Manifestations
0 (congenital)	In utero	Hypotonia Early respiratory failure Generalised muscle weakness Death in the first month of life*
I (Werdnig-Hoffman disease)	0-6 months	Weakness of head support Inability to sit up Hypotonia Reduction of reflexes Respiratory failure Swallowing disorders Death in the first two years of life*
II (Dubowitz disease)	6-18 months	Progressive proximal muscle weakness Hypotonia Reduction of reflexes Restrictive respiratory failure Difficulty walking Death in the third decade of life*
III (Kugelberg-Welander disease)	>18 months	Able to walk Progressive proximal muscle weakness Normal life expectancy
IV (adult-onset)	>21 months	Mild progressive proximal muscle weakness of lower limbs Normal life expectancy

*** If** untreated.

Table 2: Disease-modifying treatments for Spinal Muscular Atrophy.

Treatment	**Onasemnogene abeparvovec**	**Nusinersen**	**Risdiplam**
Trade Name	Zolgensma	Spinraza	Evrysdi
FDA approval	May 2019	December 2016	August 2020
EMA approval	June 2020	April 2017	February 2021
Mechanism of Action	Gene therapy with self-complementary AAV9 with human coding SMN1, leading to the production of SMN protein from SMN1 transgene.	Antisense oligonucleotide specific to ISSN1 in intron 7 of SMN2, modulating the splicing of the SMN2 pre-mRNA, thus augmenting the expression of functional SMN protein.	Small-molecule compound that targets two regions (TSL2 and ESE2) on exon 7 of the SMN2 gene and modulates SMN2 pre-mRNA splicing within the nucleus, leading to increased levels of functional SMN protein.
Indication (per EMA)	SMA patients with a biallelic mutation in SMN1 and a clinical diagnosis of spinal muscular atrophy type I or up to three SMN2 copies	SMA patients	SMA patients with a clinical diagnosis of SMA Type I, Type II or Type III or with one to four SMN2 copies
Route of Administration	single-dose, intravenous infusion; intrathecal administration under investigation	Intrathecal administration	Oral
Dose	1.1 x 10^{14} vg/kg	12mg per administration (4 loading doses on days 0, 14, 28 and 63, and then once every 4 months)	Stratified by age and body weight
Cost	≈ €1.7 million per dose	≈ €72,000 per dose	≈ €20,000 per month (adult SMA patient)

FDA: Food and Drug Administration; EMA: European Medicine Agency.

SINGLE FIBER ELECTROMYOGRAPHY IN ORBICULARIS OCULI AND FRONTALIS: RELATIVE SENSITIVITY IN MYASTHENIA GRAVIS

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Abstract

Objectives: The sensitivity of Single Fiber Electromyogram for the diagnosis of neuromuscular transmission disorders is high. The facial muscles usually tested are Orbicularis oculi and Frontalis. In this study we investigated the relative sensitivity of these two muscles in myasthenia gravis

Methods: The patients are divided in 3 groups: Patients with ocular symptoms (ptosis and/or diplopia) (group 1), with bulbar and/or limb weakness (group 2) and in clinical remission (group3). SFEMG was performed with a concentric needle electrode using voluntary activation. Mean consecutive difference and upper normal values for individual fiber pairs are compared with our normal values

Results: A total of 51 consecutive myasthenia gravis patients are recruited: 22 male and 29 female, mean age 56.3±17.3 years. The sensitivity of Orbicularis oculi is found 76.9 and of Frontalis 68.6. Combining the two muscles, their sensitivity reaches 86.5%. Both muscles are found more frequently abnormal in group 2. In group 1 we observed significantly more frequently abnormal jitter values in those with both ptosis and diplopia.

Discussion: Both facial muscles show high sensitivity in the diagnosis of Myasthenia gravis and both are complementary in the diagnosis of neuromuscular junction diseases. We propose Orbicularis oculi as the first muscle to be tested.

Key words: Single fiber Electromyogram, Myasthenia gravis, Orbicularis oculi, Frontalis

Η ΕΥΑΙΣΘΗΣΙΑ ΤΟΥ ΗΛΕΚΤΡΟΜΥΟΓΡΑΦΗΜΑΤΟΣ ΜΟΝΗΡΟΥΣ ΜΥΙΚΗΣ ΙΝΑΣ ΣΤΟ ΣΦΙΓΚΤΗΡΑ ΤΩΝ ΒΛΕΦΑΡΩΝ ΚΑΙ ΣΤΟ ΜΕΤΩΠΙΑΙΟ ΣΤΗ ΔΙΑΓΝΩΣΗ ΤΗΣ ΜΥΑΣΘΕΝΕΙΑΣ

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Περίληψη

Εισαγωγή: Η ευαισθησία του ηλεκτρομυογραφήματος μονήρους μυικής ίνας στη διάγνωση των διαταραχών της λειτουργίας της νευρομυικής σύναψης είναι υψηλή. Οι μυς του προσώπου οι οποίοι συνήθως ελέγχονται είναι ο Σφιγκτήρας των βλεφάρων και ο Μετωπιαίος. Σε αυτή τη μελέτη συγκρίναμε την ευαισθησία της εξέτασης των δύο αυτών μυών στη μυασθένεια.

Υλικό-Μέθοδος: Οι ασθενείς χωρίστηκαν σε 3 ομάδες: Ασθενείς με οφθαλμικά συμπτώματα (πτώσις βλεφάρωνή/και διπλωπία) (1η ομάδα), με προμηκικά συμπτώματα ή/και αδυναμία άκρων (2η ομάδα), ασθενείς σε κλινική ύφεση (3η ομάδα). Η εξέτασις έγινε με ομόκεντρο βελονοειδές ηλεκτρόδιο με εκούσια σύσπαση.Ο μέσος όρος συνεχόμενης διαφοράς (MCD) και η ανώτερη φυσιολογική τιμή για κάθε ζεύγος ινών συγκρίθηκαν με τις φυσιολογικές τιμές του εργαστηρίου μας.

Αποτελέσματα: Στη μελέτη περιελήφθησαν 51 ασθενείς με τη σειρά εμφάνισης στο εργαστήριο, 22 άνδρες και 29 γυναίκες μέσης ηλικίας 56,3±17,3 ετών. Η ευαισθησία του Σφιγκτήρα των βλεφάρων ήταν 76,9 και του Μετωπιαίου 68,6. Σε συνδυασμό των δύο μυών η ευαισθησία ήταν 86,5. Η ευαισθησία και των δύο ήταν μεγαλύτερη στη 2η ομάδα. Στην 1η ομάδα η ευαισθησία ήταν μεγαλύτερη στους ασθενείς με πτώση βλεφάρων και διπλωπία.

Συζήτηση: Και οι δύο μυς έδειξαν υψηλή ευαισθησία στη διάγνωση της μυασθένειας. Και οι δύο είναι συμπληρωματικοί στη διάγνωση των διαταραχών της λειτουργίας της νευρομυικής σύναψης. Προτείνουμε το Σφιγκτήρα των βλεφάρων σαν τον πρώτο μυ για το Ηλεκτρομυογράφημα μονήρους μυικής ίνας.

Λέξεις- κλειδιά: Μυασθένεια, Ηλεκτορμυογράφημα μονήρους μυικής ίνας, σφιγκτήρας βλεφάρων, μετωπιαίος

Introduction:

Single fiber Electromyography (SFEMG) is the most sensitive method for evaluating neuromuscular transmission among all the diagnostic tests when performed in a weak muscle: Sensitivity 75%-98% for generalized myasthenia gravis (GMG) and 62%-100% for ocular (OMG) and approximately with the same specificity [1-5] Orbicularis oculi (OOc) and Frontalis (Fr) are the muscles usually tested in patients with suspected MG and ocular symptoms (ptosis and/or diplopia). As far as we know, there are only a few studies comparing the relative sensitivity of these two muscles [6-7]

In this study we checked SFEMG relative sensitivity of OOc and Fr in myasthenia gravis (MG) patients.

Material and methods:

Consecutive patients with myasthenia gravis were included prospectively in the study. The diagnosis of MG was definite and was based on the following criteria: Symptoms of fluctuating muscle weakness and objective weakness on clinical examination and one of the following: 1. Elevated acetylcholine receptor (AchR) antibodies or antibodies to muscle-specific tyrosine kinase (MuSK). 2. Abnormal single-fiber electromyogram (SFEMG) in one muscle. 3. Abnormal repetitive nerve stimulation (RNS) in at least one symptomatic muscle (minimum 10% decrement in the compound muscle action potential amplitude). 4. Response to pyridostigmine therapy.

The patients were divided in 3 groups: Patients with ocular symptoms (ptosis and/or diplopia) (group 1), with bulbar and/or limb weakness (group 2) and asymptomatic, in clinical remission (group3).

For the electrophysiological study a Keypoint NET, Medtronic, Skovlunde, Denmark apparatus was used. SFEMG was performed with a concentric needle electrode 0.3 mm diameter,30 Gauss (Alpine biomed Aps Skovlunde Denmark) using voluntary activation. Amplifier filters 500Hz-10KHz, sweep velocity 1ms/div and amplitude 200 μV/div. For each pair 50 -100 traces were recorded for analysis and 20 pairs were obtained from each muscle. Acceptable pairs were those with amplitude of at least 50μV and rise time less than 300μs. Jitter was considered abnormal when 1. Mean consecutive difference (MCD) exceeded our normal values for each muscle (OOc > 27.2 μs, Fr > 29.8 μs). 2. More than 2/20 pairs MCD exceeded our upper normal values for individual fiber pairs (OOc > 38.7μs, Fr >42.1 μs) [9]. 3. When blocking was present in at least 1/20 pairs [10]. jitter value less than 5μs were non accepted [11]. The criteria for accepted waveforms proposed from Stalberg et al [12] are adopted.

Anticholinesterase medication was withheld 12 h prior to testing and skin temperature was maintained between 32-34°C. Written informed consent was obtained from participants and the study was approved from our local ethics committee (319/ 2/6/2017).

Descriptive statistics were used for quantitative presentation of the variables. 2 x 2 or 3 x 2 contingency tables were employed in order to test for frequency dependencies in categorical variables by means of Pearson's chi-squared tests. This analysis was also applied to the 3 x 2 matrix of the "MG-symptoms x SFEMG result" table, which was based on a rather small sample of muscles. Despite the fact that chi-square statistics may yield less consistent results with such small samples, it was not feasible to employ Fisher's exact test, since the latter is only indicated in 2 x 2 matrices. Finally, Cohen's kappa statistic was used to investigate the agreement between OOc and Fr SFEMG results. Significance was set at 0.05.

Results: The demographic characteristics of the study population are shown in table1. A total of 51 patients were tested: 22 male and 29 female, mean age 56.3±17.3 years (range 14-81). AchR antibodies positive were 37 patients (72.6 %), MuSK antibodies positive were 4 (7.8%) and seronegative 10 (19.6%), 9 of which had abnormal jitter in OOc and/or in Fr and one had fluctuating ocular symptoms (ptosis) compatible with MG and response to therapy.

In group 1 were included 26 patients, 17 in group 2 and 8 in group 3. Both muscles are found more frequently abnormal in group 2 (P< 0.01). The sensitivity of OOc is found 76.6%, of Fr 68.6% and combining the two muscles, their sensitivity reaches 86.5% (Table 1). A slight but not significant superiority of OOc versus Fr is noted in subgroups.

In group 1 abnormal jitter in OOc was observed in 10 out of 12 patients with both diplopia and ptosis (83.3%), and in Fr in 6 (50%) (P< 0.01). Of the 10 patients with ptosis, jitter in OOc was abnormal in 5 patients (50%) and in Fr in 6 (60%). There were 4 patients with diplopia, and jitter in OOc was abnormal in all 3 (75%) and in Fr in 2 (50%). In all 3 patients with MuSK antibodies, jitter was abnormal in both muscles.

In group 3 we found abnormal jitter in OOc in 62.5% and in Fr in 50% and in combination of the two muscles 87.5%.

Kappa agreement between OOc and Fr was 0.321 (fair agreement), p<0.05.

Table 1. Demographic data of the 51 patients and abnormal jitter in the subgroups of MG

Age mean, SD, (Range)		56.3±17.3 (17-81)				
Abs n, (%)		Ach 37(72.5)	MuSK 4 (7.8)	Seronegative 10 (19.6)		
Sex, n		Male=22	Female=29			
Abnormal jitter, n, (%)	**Total** n=44 (86.3)	**Ocular MG** 26 (51)	**Generalized MG** 17 (33,3)	**In Clinical remission** 8 (15.7)	**P value**	**Sensitivity**
OOc n, (%)	39(76.5)	17 (65.4)	17 (100)	5 (62.5)	<0.001	76.5%
Fr. n, (%)	35(68.6)	15 (57.7)	16 (94.1)	4 (50)	<0.001	68.6%
OO + Front n, (%)	30(58.8)	11 (42.3)	16 (94.1)	3 (37.5)	<0.001	86.5%

Fr=Frontalis, OO= Orbicularis oculi

Discussion:

We prospectively investigated jitter relative sensitivity of two facial muscles in MG patients: OOc. and Fr. These muscles are those more frequently investigated, especially in OMG and their sensitivity, alone or in combination, is found 70-100% [3-8]. More studies compare one facial muscle with extensor digitorum communis.

Relative sensitivity of the two facial muscles is reported in a few studies. Valls canals et al [6] found SFEMG of the OOc more sensitive for the diagnosis of OMG than of Fr. Coumouydjian et al [7] reported Fr slightly more sensitive than OOc.

In this study we could not find any statistically significant difference between the two muscles, although a slight superiority of OOc is noted in all subgroups of MG patients.

Both muscles were found more frequently abnormal in GMG than in OMG and this is noted in previous also studies. Abraham [13] reported that higher jitter (>100 ls) and higher decrement (>10%) values in RNS were more frequent in GMG. Koumouydjian et al [7] found OOc being most abnormal in GMG and Fr in OMG and combining the two muscles, jitter was slightly more abnormal in OMG than in GMG (100% versus 92.9%). Morren et al [5] found SFEMG sensitivity 73% in OMG and 85% in GMG. Sanders and Howard [2] also found more abnormal jitter in GMG than in OMG (86-100% versus 78%). Jitter is also frequently abnormal in patients in clinical remission. Sanders and Howard [2] found abnormal jitter values in facial muscles in 64% of their patients in clinical remission.

In the subgroup of patients with ocular symptoms we observed significantly more frequently abnormal jitter values in those with both ptosis and diplopia than in those with ptosis only and OOc significantly more abnormal in the patients with ptosis and diplopia, while Fr is found slightly more abnormal in those with ptosis only. Our previous study [14] and also the study of Batocchi et al [15] have shown that the presence of both diplopia and ptosis is more likely due to MG rather than to other diseases. Abraham et al [13] showed that MG patients with higher jitter values in Fr more frequently had a combination of ptosis and impaired extraocular movements. Mittal et al [16] also noted that patients with OMG who were transformed to GMG were those with both diplopia and ptosis, and no one with isolated ptosis or diplopia.

SFEMG is the most sensitive electrodiagnostic test for the diagnosis of MG, but it requires experienced personnel and patient cooperation. In this study we found high sensitivity of jitter (94-100%) for both muscles in GMG and significantly lower in the other two groups. As shown with Cohen's Kappa agreement between OOc and Fr, both muscles are complementary in the diagnosis of MG and we propose OOc as the first muscle to be tested in both OMG and GMG.

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CONTINUOUS INTESTINAL INFUSION OF DUODOPA CAN AMELIORATE THE MOTOR AND NON-MOTOR COMPLICATIONS ASSOCIATED WITH ADVANCED PARKINSON'S DISEASE

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Abstract

Advanced Parkinson's disease (PD) is associated with significant motor and non-motor complications. Motor complications include fluctuations, dyskinesias and unsteadiness and falls, whereas non-motor complications include dysarthria, dysphagia, dysautonomia, psychosis and cognitive decline. In advanced Parkinson's disease continuous intestinal infusion of levodopa/carbidopa (Duodopa) gel has been approved for ameliorating PD-related motor complications. Here, we present the data from five patients who underwent placement of Duodopa pump for advanced PD and were evaluated with the Unified Parkinson's Disease Rating Scale (UPDRS) prior to and two days after Duodopa pump initiation. These patients met the typical criteria for intestinal Duodopa infusion. This analysis revealed that the overall performance and ability to perform activities of daily living were significantly improved, and motor complications were significantly ameliorated with Duodopa treatment as compared to per os treatment. None of the patients presented a serious complication following Duodopa placement. Continuous intestinal infusion of Duodopa is therefore beneficial and acceptably safe in advanced Parkinson's disease given that the indications and contraindications for this method are considered.

Keywords: Advanced Parkinson's disease, levodopa/carbidopa (Duodopa), motor complications, fluctuations, dyskinesias

Η ΣΥΝΕΧΗΣ ΕΝΔΟΝΗΣΤΙΔΙΚΗ ΕΓΧΥΣΗ DUODOPA ΜΠΟΡΕΙ ΝΑ ΒΕΛΤΙΩΣΕΙ ΤΙΣ ΚΙΝΗΤΙΚΕΣ ΚΑΙ ΜΗ ΚΙΝΗΤΙΚΕΣ ΕΠΙΠΛΟΚΕΣ ΠΟΥ ΣΧΕΤΙΖΟΝΤΑΙ ΜΕ ΤΗΝ ΠΡΟΧΩΡΗΜΕΝΗ ΝΟΣΟ PARKINSON

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Περίληψη

Η προχωρημένη νόσος Parkinson σχετίζεται με σημαντικές κινητικές και μη κινητικές επιπλοκές. Οι κινητικές επιπλοκές περιλαμβάνουν τις διακυμάνσεις, τις υπερκινησίες και αστάθεια και πτώσεις, ενώ οι μη κινητικές επιπλοκές περιλαμβάνουν δυσαρθρία, δυσφαγία, δυσλειτουργία του αυτονόμου, ψύχωση και νοητική έκπτωση. Στην προχωρημένη νόσο Parkinson η συνεχής ενδονηστιδική έγχυση γέλης levodopa/carbidopa

(Duodopa) είναι εγκεκριμένη θεραπεία για την αντιμετώπιση των κινητικών επιπλοκών. Σε αυτό το άρθρο, παρουσιάζουμε τα δεδομένα από πέντε ασθενείς με προχωρημένη νόσο Parkinson που υποβλήθηκαν σε τοποθέτηση αντλίας Duodopa και εκτιμήθηκαν με την Unified Parkinson's Disease Rating Scale (UPDRS) πριν και δύο ημέρες μετά την έναρξη ενδονηστιδικής έγχυσης Duodopa. Οι ασθενείς πληρούσαν τα κριτήρια τοποθέτησης αντλίας Duodopa. Αυτή η ανάλυση έδειξε ότι η θεραπεία με Duodopa οδήγησε σε βελτίωση της γενικής επίδοσης και της ικανότητας επιτέλεσης καθημερινών δραστηριοτήτων, και σε ελάττωση των διακυμάνσεων και των υπερκινησιών, συγκριτικά με την αγωγή από το στόμα. Κανένας από τους ασθενείς δεν παρουσίασε σοβαρή επιπλοκή. Η συνεχής εντερική έγχυση Duodopa είναι συνεπώς αποτελεσματική και σχετικά ασφαλής στην προχωρημένη νόσο Parkinson, εάν τηρηθούν οι ενδείξεις και οι αντενδείξεις της μεθόδου.

Λέξεις Ευρετηρίου: Προχωρημένη νόσος Parkinson, λεβοντόπα/καρβιντόπα (Duodopa), κινητικές επιπλοκές, διακυμάνσεις, υπερκινησίες

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by progressive dysfunction and loss of dopaminergic neurons that reside in substantia nigra pars compacta (SNc) and project to the striatum (nigrostriatal pathway) which is the input nucleus of basal ganglia[1,2]. This degeneration greatly impairs the balance between excitation and inhibition in basal ganglia neuronal circuits, resulting in loss of spontaneous movements and hypokinesia[3]. Despite that idiopathic PD responds to dopaminergic therapy at early stages, at advanced stages PD presents with progressively lower response to levodopa and presents with motor fluctuations, dyskinesias, truncal symptoms that include unsteadiness and falls, dysarthria and dysphagia as well as psychosis and cognitive decline[4]. Motor complications of advanced PD result from fluctuating levels of per os administered levodopa, which when it is present at high levels can lead to dyskinesias and when it is present at low levels can lead to "OFF state". In addition, in PD patients, gastric emptying is delayed, impacting directly the absorbance and bioavailability of orally administered medications that have intestinal absorption. As a result, with disease progression fluctuations and dyskinesias are difficult to manage and become refractory to per os therapeutic manipulations[4]. The continuous intestinal infusion of Duodopa through a portable infusion pump has been approved as a standard of care for advanced PD when certain indications are met, with the most important of these being the good response to levodopa (satisfactory "ON state"), in the absence of contraindications. Levodopa/ carbidopa enteral suspension is marketed as Duodopa outside the United States (U.S.) and it was approved by the European Medicines Agency in 2004, while in the U.S. it is marketed as Duopa and it was approved by the U.S. Food and Drug Administration (FDA) on January 12th 2015; the latter was based on a Phase 3, 12-week, double-blind, double-placebo, multi-center trial that compared the efficacy and safety of Duopa to oral levodopa-carbidopa tablets in advanced Parkinson's disease patients. Here, we present the data from five patients who were placed on Duodopa intestinal infusion for advanced PD at our tertiary center and emphasize the multifaceted clinical benefit of this method in these patients.

Methods

Patients: Five patients with advanced PD who have had good prior response to levodopa and at late disease stages displayed motor fluctuations and dyskinesias despite optimal per os treatment, and without major non-motor disease complications, underwent placement of Duodopa intestinal infusion pump at our hospital, in a collaborative effort by Parkinson's disease outpatient center, the Neurology Clinic, and the Gastroenterology Department. Advanced PD patients met the '5-2-1' criteria for advanced PD[5]. Patients underwent neurologic evaluation before and after the placement of Duodopa infusion pump, which included quantification of PD-associated symptoms and signs with the Unified Parkinson's Disease Rating Scale (UPDRS). UPDRS total scores and sub-scores for UPDRS parts I (UPDRS-I), II (UPDRS-II), III (UPDRS-III) and IV (UPDRS-IV) of this scale, which evaluate mood/cognition/ behavior, daily living, motor examination and motor complications, respectively, are presented for two time points, before the placement of the pump and two days after Duodopa initiation. All evaluations were performed at the "ON state" for both per os treatment and for Duodopa. "ON" state is defined as the state in which PD patients have good mobility, as this has been defined previously[6,7]. After Duodopa initiation, all PD medications were discontinued except for dopamine receptor agonists.

Endoscopic procedure: The placement of nasojejunal tube (NJ) and percutaneous endoscopic gastrostomy with jejunal extension (PEG-J) were performed at the endoscopic department following standard procedures. All patients underwent rigorous cardiological and anesthetist evaluation before PEG-J. The

patients had no contraindications for endoscopic PEG tube placement. Prior to the procedure, written informed consent was obtained from all patients and detailed information regarding the procedure itself and the post-procedure tube care was given to both patients and caregivers. All five patients underwent placement of a temporary nasojejunal tube as a treatment evaluation test for a period of three days before the placement of the permanent gastrojejunal tube. The latter consisted of the placement of a 15 French Freka PEG tube via the "pull" technique, through which a 9 French Freka J-tube was inserted during the same procedure. The jejunal tube was placed into the distal duodenum/proximal jejunum by grasping the tube tip with a forceps and then advancing the endoscope. The scope was slowly withdrawn into the stomach while the forceps were advanced to hold the tip of the J-tube in place. Once the endoscope was in the stomach, the forceps were opened, releasing the jejunal tube. One patient presented desaturation at the beginning of the endoscopic procedure and was intubated, followed by detubation at the end of the procedure with immediate and complete recovery.

Graphs and statistics: Data collection and generation of graphs were performed in

GraphPad Prism. Figure assembly was performed in Adobe Illustrator. Formal statistical analysis was not performed for these five patients because of the small size of the sample that would make the power of statistical analysis quite low. Descriptive statistics is provided. Data are presented in three types of graphs: one graph shows all patients on per os treatment and on Duodopa in which absolute values of each sub-scale are presented (a dashed line connects the two values for each patient), one graph shows the change between per os treatment and Duodopa for each patient (each patient is denoted by a different symbol) and an improvement is reflected in negative values, and another graph shows the response rate for each patient (each patient is denoted by a different symbol) and an improvement is reflected in positive values. Response rate % is calculated as the ratio $\Delta UPDRS/UPDRS_{initial}$ ($UPDRS_{initial}$, per os treatment) x100.

Results

Effect of Duodopa on overall performance of patients with advanced Parkinson's disease

Five patients with advanced PD were placed in treatment with Duodopa intestinal infusion pump, while per os treatment for PD was discontinued (see Methods). The overall motor and non-motor performance and the ability to perform activities of daily living were evaluated with the UPDRS before and two days after Duodopa initiation. Evaluations at both time points were performed at the "ON state". Despite the small size of our sample that prevents a detailed statistical analysis, there seems to be a beneficial effect of Duodopa on the overall state and performance of PD patients, compared to their respective state while receiving optimal oral treatment (Figure 1). This is reflected in the lower total score of UPDRS (Figures 1A-C) and the lower sub-score of UPDRS-II (Figures 1D-F) achieved with Duodopa treatment compared to oral treatment. Of note, there also seems to be a positive effect of Duodopa on mood and behavior during the "ON state", as compared to per os treatment (Figure 2).

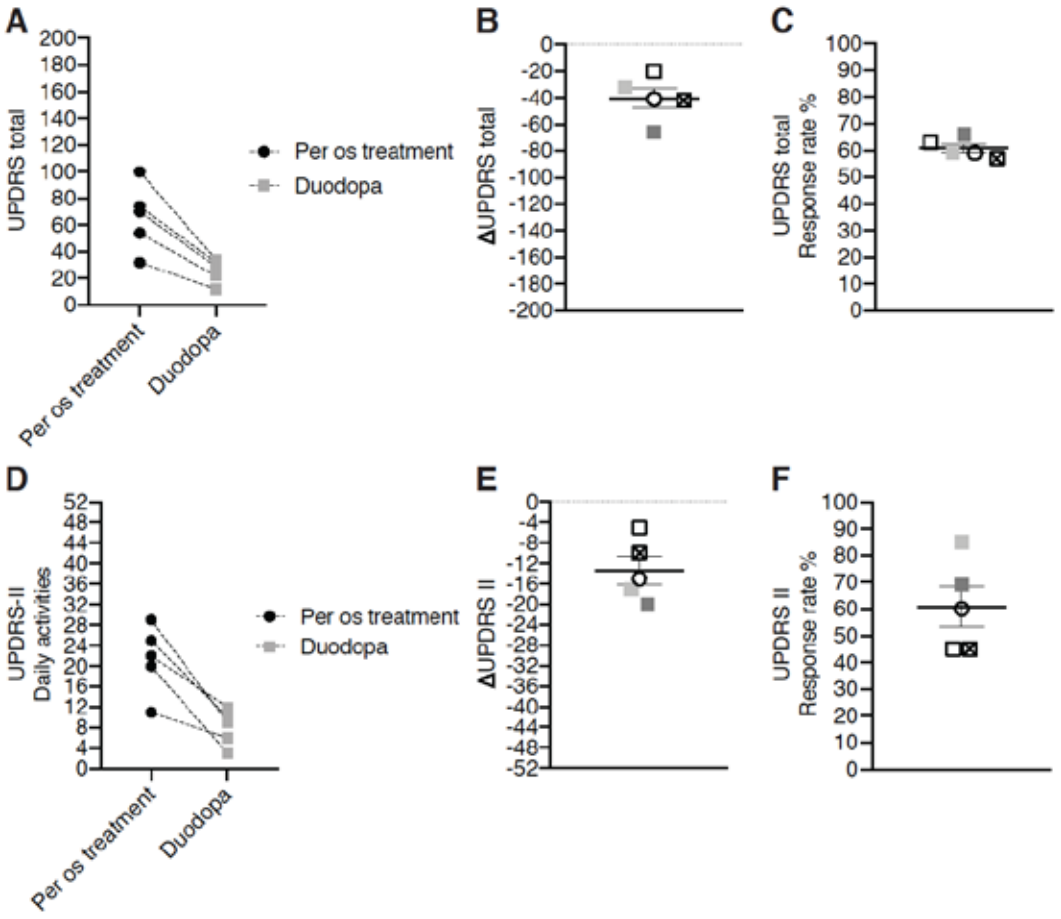

Figure 1. Effects of treatment with Duodopa intestinal infusion on overall performance and state of patients with advanced PD.

(A-C) Duodopa may improve overall performance of PD patients. (A) UPDRS total score before and two days after Duodopa placement for each of the five patients analyzed. Y axis extends up to 199, which is the maximum total UPDRS score. For each treatment category, each dot represents a different patient; the same patients are presented for per os treatment and for Duodopa. (B) All patients present a decrease in UPDRS total score (ΔUPDRS total) while on Duodopa compared to optimal per os treatment, which is reflected in negative values. Data are presented in a scatter dot plot with mean ± S.E.M. (S.E.M., standard error of the mean). Mean decrease is 40.2. Each patient is depicted in a different symbol, which is the same for each patient across all graphs presenting a change (Δ) in this article. (C) Total UPDRS response rate, expressed as %, is calculated as the difference between final and initial total UPDRS score divided by the initial score x100 (see Methods).

(D-F) Duodopa may improve the ability to perform activities of daily living, as reflected in UPDRS-II subscale. (C) UPDRS-II score before and two days after Duodopa placement. Y axis extends up to 52, which is the maximum UPDRS-II score. (D) All patients present an improvement in their daily activities with Duodopa treatment compared to per os treatment. Data are plotted in a scatter dot plot with mean ± SEM. Mean decrease is 13.4. (F) UPDRS II response rate, calculated as explained above.

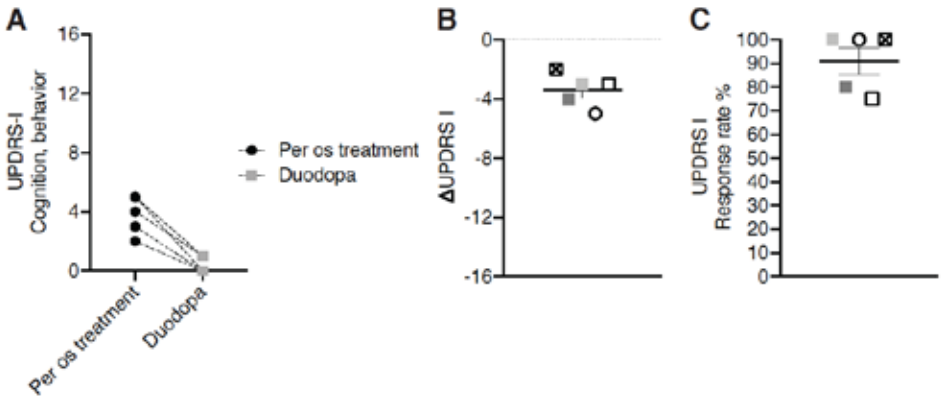

Figure 2. Effects of treatment with Duodopa intestinal infusion on emotional and behavioral deficits associated with advanced PD.

(A-C) Duodopa may ameliorate emotional and behavioral symptoms associated with advanced PD. (A) Mood and behavior, as reflected in UPDRS-I subscale, before and two days after Duodopa placement. Y-axis extends up to 16, which is the maximum UPDRS-I score. (B) All patients display an improved behavioral and emotional profile following Duodopa treatment compared to per os treatment. Data are plotted in a scatter dot plot with mean ± SEM. Mean decrease is 3.4. (C) UPDRS I response rate, calculated as explained above.

Effect of Duodopa on motor deficits associated with advanced Parkinson's disease

Evaluation of PD patients with motor examination for motor performance and motor complications, showed that there is a positive effect of Duodopa on motor performance at the "ON state", compared to per os treatment at the "ON state" (Figures 3A-C). The more modest effect of Duodopa on motor performance as this is reflected in UPDRS-III is attributed to the optimization of per os treatment before Duodopa initiation and also to the timely placement of Duodopa pump in late-stage PD. In addition to evaluating the motor performance overall, we assessed the patients for motor complications including fluctuations and dyskinesias, as these are reflected in UPDRS-IV. This assessment showed that there is a strong effect of Duodopa treatment on motor complications compared to per os treatment (Figures 3D-F). Next, we assessed the effect of Duodopa separately on fluctuations and dyskinesias. This analysis revealed that both fluctuations and dyskinesias may be ameliorated with continuous intestinal Duodopa infusion, compared to per os treatment (Figures 4A-F).

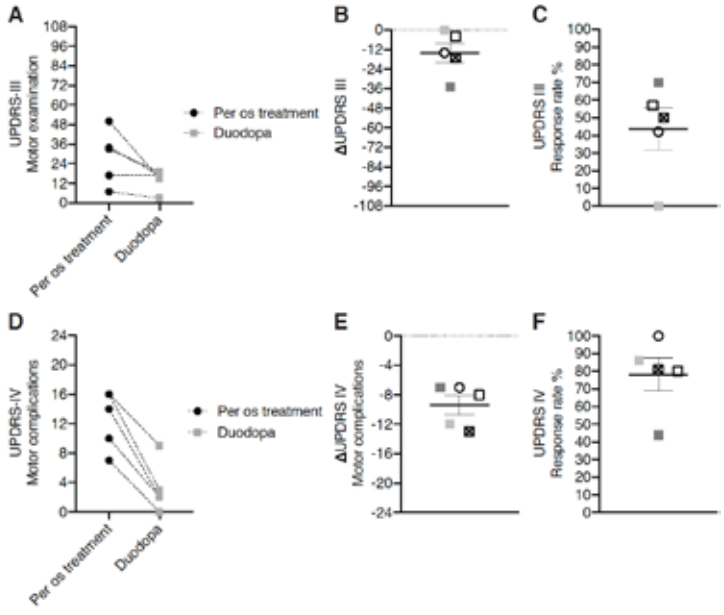

Figure 3. Effects of Duodopa intestinal infusion on motor performance and motor complications in advanced PD.

(A-C) Duodopa may improve motor performance, compared to optimal per os treatment, in advanced PD patients. (A) Motor skills, reflected in UPDRS-III sub-scale, before and two days after Duodopa placement. Y axis extends up to 108, which is the maximum UPDRS-III score. (B) All patients display improved motor skills following Duodopa treatment compared to optimal per os treatment, as reflected in the decrease in UPDRS-III score. Data are plotted in a scatter dot plot with mean ± SEM. Mean decrease is 14. (C) UPDRS III response rate.

(D-F) Effects of Duodopa on PD-associated motor complications (both fluctuations and dyskinesias). (C) Motor complications, reflected in UPDRS-IV sub-scale, before and two days after Duodopa placement. Y axis extends up to 23, which is the maximum UPDRS-IV score. (D) All patients display diminished PD-related motor complications following Duodopa treatment compared to optimal per os treatment, as reflected in the decrease in UPDRS-IV score. Data are plotted in a scatter dot plot with mean ± SEM. Mean decrease is 9.4. (F) UPDRS IV response rate.

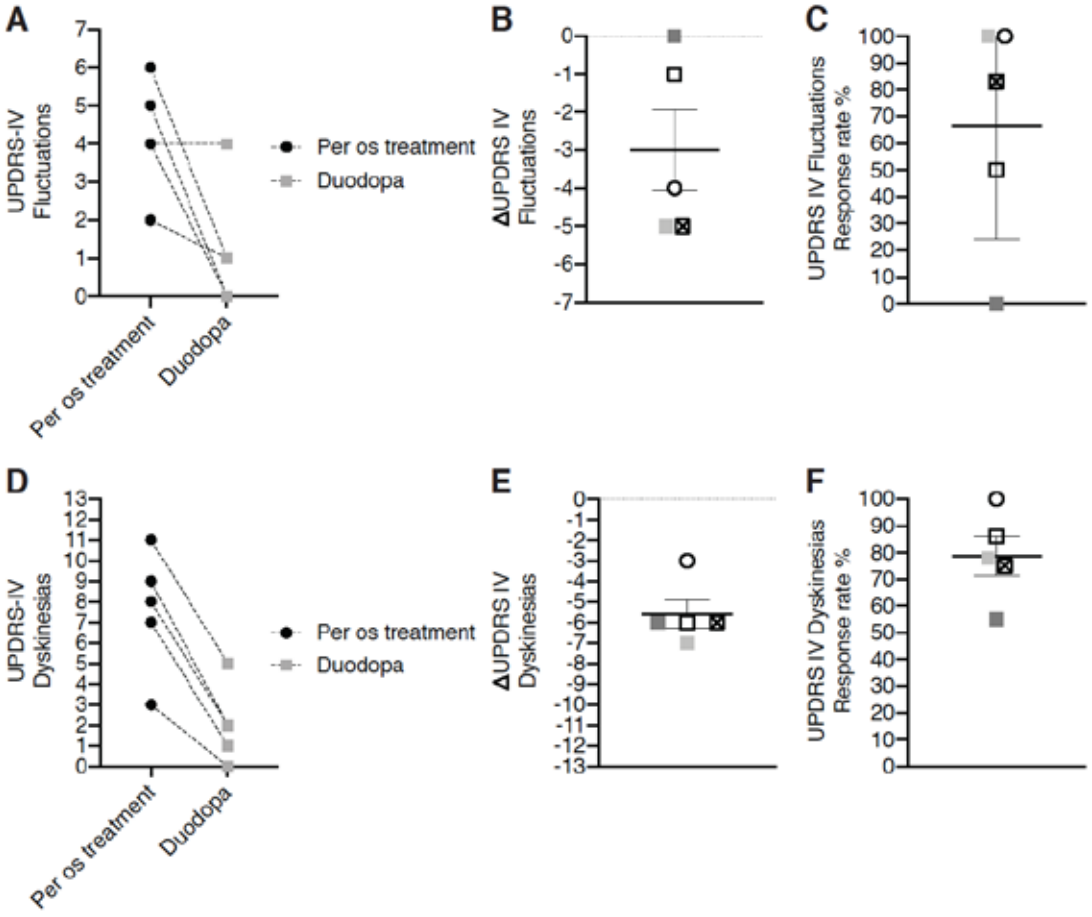

Figure 4. Effects of Duodopa intestinal infusion on fluctuations and dyskinesias in advanced PD.

(A-C) Effects of Duodopa on PD-associated motor fluctuations. (A) Motor complications, reflected in UPDRS-IV sub-scale, before and two days after Duodopa placement. Y axis extends up to 7, which is the maximum UPDRS-IV sub-score for motor fluctuations. (B) All patients display diminished PD-related motor fluctuations following Duodopa treatment compared to optimal per os treatment. Data are plotted in a scatter dot plot with mean ± SEM; Mean decrease is 3. (C) UPDRS IV response rate of fluctuations.

(D-F) Effects of Duodopa on PD-associated dyskinesias. (C) Motor complications, reflected in UPDRS-IV sub-scale, before and two days after Duodopa placement. Y axis extends up to 13, which is the maximum UPDRS-IV sub-score for dyskinesias. (D) All patients display diminished PD-related dyskinesias following Duodopa treatment compared to optimal per os treatment. Data are plotted in a scatter dot plot with mean ± SEM; Mean decrease is 5.6. (F) UPDRS IV response rate of dyskinesias.

Optimization of Duodopa intestinal infusion

Duodopa is usually administered with a 16-hour infusion during daytime. Less frequently, Duodopa

infusion is maintained during the night in case it is needed. Of the five patients placed on Duodopa that are presented here, one needed 24-hour infusion to avoid dystonia and freezing associated with the "OFF state" during the night. This is in agreement with previous studies reporting the need for all-day Duodopa administration in a select subset of patients[8]. Moreover, given that most PD patients have worse status in the afternoon and at night, our experience has shown that biphasic titration can work for optimal Duodopa dosage for controlling motor fluctuations and dyskinesias, given the inherent diurnal variability of disease-related symptoms. Moreover, the "dose failure" effect usually seen with per os treatment, was seen intensely in one of our patients, which was surpassed with the administration of an extra dose half an hour before a rich meal.

Safety of Duodopa infusion pump

Duodopa pump treatment may have short-term and long-term complications and/or side-effects. These may be associated with the procedure or the infusion of Duodopa. The vast majority of PEG-J-related complications occur in the first month. Given the short follow-up of our patients (a few months long) following Duodopa initiation, only short-term complications can be presented here. Among our patients with Duodopa pump, one presented with local skin infection around the tube's entry site that resolved with local application of mupirocin cream and another one presented with pneumoperitoneum that resolved after a couple of days with a short course of antibiotics. Moreover, all of our patients presented a transient increase in serum markers of inflammation, mostly asymptomatic. Therefore, percutaneous endoscopic gastrostomy-mediated Duodopa administration seems to be quite safe, in accordance with previous reports[9]. These data are reassuring for advanced PD-affected individuals that choose to follow this type of treatment at the late stages of their disease.

Discussion

Late stage PD is difficult to manage because of the multitude of non-motor symptoms that are variably responsive to treatment, and because of the motor symptoms that result from the advanced degeneration of the dopaminergic system and the non-continuous levodopa administration per os, which both account for peak-dose and end-of-dose side-effects[4]. Duodopa intestinal infusion pump is an approved treatment for motor complications of late stage PD. Our data support the notion that continuous intestinal infusion of Duodopa can mitigate advanced PD-associated morbidity and in particular fluctuations, dyskinesias, and mood and behavioral deficits related to the "OFF state", in accordance with the results of similar studies reported elsewhere[10–14]. This is due to the fact that Duodopa pump reduces L-dopa level fluctuations in plasma leading to reduced motor complications. Our results are in accordance with the results of the largest international, prospective, 54-week, open-label LCIG study. In addition, it has been shown a significant benefit for the quality of life of PD patients and their caregivers[16].

According to our experience, rigorous titration is needed in order to achieve maximal clinical benefit of Duodopa. This includes optimization of continuous dose, which may be different during the day and in the afternoon until Duodopa shutoff, optimization of the morning dose, optimization of extra doses to achieve best motor performance tailored to the needs of individual patients in the absence of debilitating dyskinesias, regulation of the infusion interval (16-hour or 24-hour), and manipulations to minimize dose failure following protein-rich meals.

In our analysis, it is evident that besides motor complications, non-motor symptoms of advanced PD, as these are reflected in UPDRS-I scores, can also be ameliorated with continuous Duodopa intestinal infusion. Although this could be a direct result of the elimination of "OFF states" or be due to the fact that non-motor symptoms were mild, given that UPDRS scoring for both pre-Duodopa and on Duodopa periods was performed at the "ON state", it is possible that effects of Duodopa on brain circuitry controlling mood and behavior account for this non-motor improvement. The latter could be explained by the robust anatomical and functional bidirectional coupling of the circuits that control motor performance with the circuits that control cognition and emotional states[17–19]. In particular, functional disconnection between cognitive control networks and basal ganglia networks has been associated with freezing of gait in patients who were walking and at the same time were performing a cognitive task[19]..Similarly, in PD patients who perform dual task, cognitive and motor, a cognitive error may lead to loss of balance, which is not observed in healthy control subjects [20]. Further, reduced function in executive-attention network and in visual network at resting state has been associated with freezing of gait[21]. Of note, PD patients with freezing of gait who respond to levodopa have a better executive function than PD patients with freezing of gait unresponsive to levodopa[22]. It is therefore likely that continuous intestinal levodopa infusion exerts effects on the feedback loop between motor performance and cognitive states.

Chronic Duodopa intestinal treatment has been associated with the development of polyneuropathy, at least partially accounted for by the malabsorption of complex B vitamins[23]. It is prudent that patients placed on Duodopa treatment are followed up for

signs of polyneuropathy and levels of vitamins.

Given the therapeutic benefit of continuous Duodopa infusion, there have been taking place intense efforts to develop levodopa/carbidopa administered continuously via the subcutaneous route. It seems that this method can achieve good levodopa levels and similar therapeutic benefit[24]. Moreover, subcutaneous levodopa administration is associated with better tolerance because it has fewer side-effects since it is minimally invasive and does not have the high weight of Duodopa pump that the patients need to carry. Provided that PD is a chronic and progressive debilitating disease, the endeavors that point toward the development of continuous subcutaneous Duodopa administration should be intensified with the aim to reduce the burden related with the treatment of advanced PD.

Conflict of interest

The authors declare no conflict of interest related to the work presented here.

Ethical requirements statement

All clinical and laboratory procedures were performed according to the ethical principles for human medical research established by the Declaration of Helsinki (1964 and subsequent amendments) and in line with the "Code of Medical Ethics" (Article 62 N. 2071/1992) and "The Rights of the Nosocomial Patient" (Article 47 N. 2071/1992) of the Greek National Council on Medical Ethics (article 61 N. 2071/1992) as well as in accordance with the institutional policies of Attikon Hospital. Each and every patient has signed a written informed consent.

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ΘΕΡΑΠΕΙΑ ΙΝΙΑΚΗΣ ΝΕΥΡΑΛΓΙΑΣ ΜΕ ΤΗ ΧΡΗΣΗ ΠΑΛΜΙΚΩΝ ΡΑΔΙΟΣΥΧΝΟΤΗΤΩΝ: ΑΝΑΣΚΟΠΗΣΗ ΒΙΒΛΙΟΓΡΑΦΙΑΣ ΚΑΙ Η ΕΜΠΕΙΡΙΑ ΤΗΣ Β ΝΕΥΡΟΛΟΓΙΚΗΣ ΚΛΙΝΙΚΗΣ ΤΟΥ ΕΚΠΑ

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Περίληψη:
Εισαγωγή: Η αποτελεσματικότητα της συμπτωματικής φαρμακευτικής αγωγής στην ινιακή νευραλγία είναι συχνά περιορισμένη. Η θεραπεία ωστόσο με τη χρήση παλμικών ραδιοσυχνοτήτων, μια ελάχιστα επεμβατική διαδικασία κατά την οποία εφαρμόζονται παλμικές ραδιοσυχνότητες στα ινιακά νεύρα υπό συγκεκριμένες συνθήκες και παραμέτρους, είναι αποτελεσματική με διάρκεια κάποιες φορές πέραν των 6 μηνών. **Μέθοδοι:** Περιγράφουμε τρεις ασθενείς με ινιακή νευραλγία, ανθεκτική στις φαρμακευτικές θεραπείες, οι οποίες υποβλήθηκαν σε θεραπεία με παλμικές ραδιοσυχνότητες (PRF). **Αναφορές Περιστατικών:** Τρεις Καυκάσιες γυναίκες παρουσίασαν επίμονη κεφαλαλγία, συσφικτικού χαρακτήρα εντοπισμένη ή προερχόμενη από την ινιακή περιοχή με παροδική ύφεση του άλγους μετά από τον αποκλεισμό των ινιακών νεύρων. Το σύνολο αυτών των ασθενών έπασχαν από ινιακή νευραλγία πληρώντας τα κριτήρια της 3ης έκδοσης της Διεθνούς Εταιρείας Κεφαλαλγίας για την διάγνωσή της. Η αρχική εμφάνιση των συμπτωμάτων ήταν από τουλάχιστον 10 χρόνια πριν. Οι ασθενείς είχαν ήδη δοκιμάσει αντιφλεγμονώδη και μυοχαλαρωτικά, γκαμπαπεντίνη, πρεγκαμπαλίνη και τρικυκλικά αντικαταθλιπτικά (TCA) σε κατάλληλες δόσεις και για αρκετό χρονικό διάστημα χωρίς ικανοποιητική ανταπόκριση. Στην επανεξέταση στους 3 και στους 6 μήνες από την εφαρμογή της θεραπείας με PRF εκτός από τον πόνο και η ευαισθησία στην πίεση και την ψηλάφηση της ινιακής περιοχής ήταν μικρότερη και στις τρεις ασθενείς μας ενώ δεν παρατηρήθηκαν ανεπιθύμητες ενέργειες. Στη συνέχεια η θεραπεία επαναλήφθηκε και αναμένουμε τα νέα αποτελέσματα. **Συμπέρασμα:** Αν και απαιτούνται περαιτέρω μελέτες που να περιλαμβάνουν μεγαλύτερο αριθμό ασθενών με ινιακή νευραλγία, τα ευρήματά μας έδειξαν ότι η εφαρμογή PRF στα ινιακά νεύρα μπορεί να είναι μια αποτελεσματική θεραπευτική επιλογή για τον έλεγχο αυτής της ανθεκτικής μορφής κεφαλαλγίας.

Λέξεις Ευρετηρίου : Ινιακά Νεύρα, Ινιακή Νευραλγία, Παλμικές Ραδιοσυχνότητες, θεραπεία με Παλμικές Ραδιοσυχνότητες

PULSED RADIOFREQUENCE IN THE TRATMENT OF OCCIPITAL NEURALGIA: LITERATURE REVIEW AND SINGLE-CENTER EXPERIENCE

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Abstract:
Introduction: Even though various medications and procedures are used to treat occipital neuralgia, their effectiveness is sometimes limited. Radiofrequency pulsed therapy is a minimally invasive procedure in which the occipital nerves are treated with radiofrequency waves, a procedure that is effective, drug free and lasts for several months, often in excess of 6 months. **Methods:** We report three cases with occipital neuralgia, resistant to conservative therapies, who underwent pulsed radiofrequency therapy (PRF). **Case**

Reports: Three Caucasian women presented with persistent headache, localized or originating in the occipital region. All three patients suffered from occipital neuralgia according the International Headache Society criteria for occipital neuralgia, 3rd edition and complained of chronic tight headaches mainly located in the occipital region. Their diagnosis confirmed by undergoing an anesthetic nerve block. The initial onset of the symptoms was more than 10 years ago. The patients had already tried anti-inflammatory drugs and muscle relaxants, gabapentin, pregabalin and tricyclic antidepressants (TCA) in appropriate doses and for a sufficient period of time without satisfactory response. On re-examination at 3 and 6 months respectively, pain as well as sensitivity to pressure and palpation of the occipital region was reduced to all of our patients and no adverse effects were observed. Subsequently, the treatment was repeated and we are waiting for the results. **Conclusion:** Although further studies including a larger number of patients with occipital neuralgia are needed, our findings showed that PRF in occipital nerves may be an effective therapeutic option for the control of refractory headache.

Key words: occipital nerves, occipital neuralgia, pulsed radiofrequency, pulsed radiofrequency treatment

Introduction

Occipital neuralgia is a neurological condition that involves shooting, shocking, throbbing, burning, or aching pain, generally starting at the base of head and spreading along the scalp unilaterally or bilaterally. The scalp may become tender and extremely sensitive to the point where a light touch can cause severe pain (allodynia). Causes of occipital neuralgia include injury, pinched nerve, tight neck muscles, nerve compression, infection or inflammation [1].

Pulsed radiofrequency (PRF) is a minimally interventional pain management technique that has been effective in the treatment of chronic pain. PRF treatment is carried out by delivering a low-energy electrical field in rapid pulsations to target nervous tissue and associated microglia. PRF is not ablative, but instead neuromodulating, treating a variety of chronic neuropathic pain disorders [2].

Herein, we present three Caucasian women diagnosed with occipital neuralgia, displaying moderate or no response to all treatments indicated for their disease.

Cases description

Case 1

Patient 1 was a 78-year-old woman who visited our tertiary headache center due to occipital neuralgia over a period of 15 years. She complained of bilateral, pressing tightening pain of moderate intensity in the regions overlying the occipital nerves. She experienced about 12 episodes of headache every month. The patient had a history of arterial hypertension and hyperlipidemia, under treatment. Thorough diagnostic work-up excluded other possible etiologies.

Over the years she tried various therapeutic regiments. Acute drug therapy included simple analgesics or non-steroidal anti-inflammatory drugs (NSAIDs) such as naproxen, ibuprofen and diclofenac. She had over 10 years received amitriptyline, mirtazapine and venlafaxine without any pain relief.

We performed PRF stimulation on occipital nerves bilateral. The aseptic technique was applied during PRF procedure. The patient was maintained in the prone position. We searched occipital nerves (ON) with anatomical signs. The greater occipital nerve (GON) was found superficial to the obliquus capitis inferior muscle at this level bilaterally. The lesser occipital nerve (LON) was found at the lateral 1/3 of the external occipital protuberance to the mastoid process. After identifying the nerves, the catheter needle was inserted, and the sensory simulation test was carried out using an RF generator. The PRF treatment was administered under the constraint that the temperature of the electrode tips did not exceed 42°C for 4 minutes. This was followed by occipital nerve block with 1.5 ml of 0.5% bupivacaine and 10 mg of dexamethasone and lidocaine (Figure 1A).The patient was followed up for 6 months. There was a substantial improvement that was maintained until the 6th month. No adverse effects of the procedure were reported.

Case 2

Patient 2 was a 39-year-old woman who presented to our outpatient department for occipital neuralgia for over 10 years that was not responding to usual pharmacological treatment. Pain was sharp and shooting slightly more on the left side. Pain would travel up to the vertex, especially with the lateral bending of head. The patient did not give any history of trauma to the cervical spine or head. Her medical history was unremarkable and her routine laboratory investigations as well as brain Magnetic Resonance Imaging (MRI) were normal. She had been treated with different non-steroidal anti-inflammatory drugs, muscle relaxants as well as antidepressants without

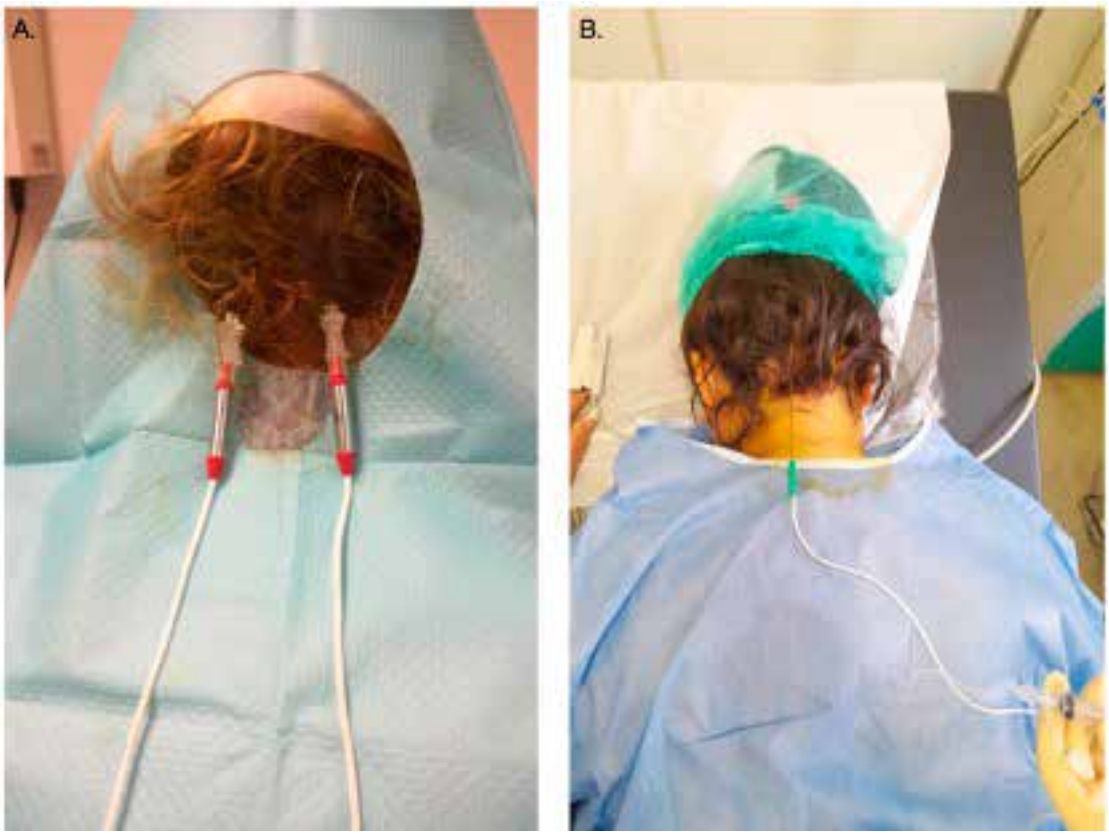

Figure 1.: PRF application in our patients

response. Neurological examination showed pain, that could be elicited by pressure on the point of distribution areas of GON.

We performed PRF stimulation on GON bilateral, in the same way as in the previous patient (Figure 1B). There was a great improvement that was maintained during the follow up period of 6 months.

Case 3

Patient 3 was an 82-year-old woman who suffered from occipital neuralgia, arterial hypertension, Meniere's disease and fibromyalgia as well as interstitial lung disease. She visited our headache center due to occipital neuralgia. She reported bilateral stabbing pain in the posterior part of scalp and apparent allodynia during innocuous stimulation of hair. She had tried various preparations including simple analgesics or non-steroidal anti-inflammatory drugs (NSAIDs) as acute drug therapy and amitriptyline, pregabalin and duloxetine in the context of prophylactic treatment. No pain relief effect had been presented.

The extensive diagnostic workout was negative for secondary causes of headache. We followed the same technique as in our aforementioned patients, without complications. There was a great improvement that was maintained throughout the follow-up period of 6 months.

Discussion

Occipital neuralgia is a neuralgiform disorder defined as paroxysmal, shooting or sharp pain in the distribution of occipital nerves. The pain originates in suboccipital region and radiates over the vertex. Hypo- or dysesthesia in the dermatome of ON, as well as tenderness to pressure over the course of ON can accompany the pain. The pain intensity is often severe and debilitating, with a negative impact on the quality of life and functionality. Most cases of occipital neuralgia are idiopathic, or in the context of various primary headaches without a clearly identifiable etiology [3]. The treatment of occipital neuralgia poses inherent challenges. Conservative treatment options such as physiotherapy and pharmacotherapy are usually tried. When occipital neuralgia is refractory to pharmacotherapy there is the alternative application of PRF to the occipital nerves, showing long-term efficacy.

PRF is a minimally invasive percutaneous technique as exposing the targeted neural structure to a train of short-duration, high-voltage radiofrequency (RF) pulses (500kHz) rather than ablation by a continuous RF current, with zero to minimal neurodegeneration and a favorable side effect profile [4]. Nerves are identified following the anatomical landmarks described in the literature, with the target point for the GON

Table 1.: Published studies reporting patients with occipital neuralgia, treated with pulsed radiofrequency

Author	Year	Number of Patients	Percentage (%) of patients with pain relief	Duration of follow up (months)
Foska A, et al.	2024	3	100	6
Cohen SP, et al.	2015	17	N/A*	6
Choi HJ, et al.	2012	10	80	7.5
Huang JH, et al.	2012	102	51	3
Vanelderen P, et al.	2010	19	52.6	6
Navani A, et al.	2006	1	100	5

*: Response was estimated as the relief (mean difference) of occipital pain favors PRF group in 3 months

being one-quarter to one-third of the distance of the line connecting the external occipital protuberance with the mastoid process, medial to the occipital artery. Similarly, for the LON, the target point is located two-thirds of the distance from occipital protuberance up to mastoid process. The accurate position of the needle is confirmed using electrical stimulation, with repeated adjustments in order to maximize nerve stimulation at the lower possible voltage (with target being < 0.4mV) [5].

To date, six studies have evaluated the pain-reducing effects of PRF on occipital nerves, showing overall favorable outcomes (Table 1). Navani et al. in 2006 described a case of a 62-year-old man with a 43-year history of left suboccipital pain where PRF of GON demonstrated 60-70% pain relief that was sustained for 4 months after initial treatment and for 5 months after the second treatment [6]. Vanelderen et al. in 2010 conducted a prospective analysis of 19 patients with ON treated with PRF with just over half of patients reporting a decrease in pain and resultant medication use [7]. In a retrospective analysis, by Huang et al. in 2012, 51% of ON patients treated with PRF reported >50% reduction in pain relief at a 3-month follow-up [8]. In a retrospective clinical study, concerning PRF neuromodulation in occipital neuralgia and consisting of ten patients, pain relief for at least 6 months was observed [9]. The efficacy of PRF of the occipital nerves was compared with steroid injections in a multicenter, randomized, double-blind, comparative-effectiveness study published in 2015 [10]. Patients had occipital neuralgia or migraine with occipital nerve tenderness. Forty-two patients received local anesthetic and normal saline followed by three cycles of PRF treatment per targeted nerve. Thirty-nine patients received local anesthetic mixed with steroid and three cycles of sham PRF. Six weeks later, pain reduction was significantly greater in PRF group compared to steroid group; this persisted through the 6 months follow-up [10]. The most recent study was an observational, open-label, prospective study, describing fifty-seven patients suffering from chronic headache including, chronic migraines, cluster headaches, tension-type headaches, and occipital neuralgia. Participants underwent PRF, which improved the number and the pain intensity of headache episodes per month [11].

The mechanisms underlying the pain relief following PRF stimulation have not been clearly demonstrated. Published data suggest that PRF modulates the early gene c-Fos, which is responsible for the development of the second m-RNA, "preprodinorphin", of the endogenous opioid system. PRFs analgesic properties are also mediated through the noradrenergic, serotonergic, and endogenous opioid inhibitory pain pathway, suggesting peripheral and central modulating action [12]. Another theory suggests that it is achieved by applying a low-intensity electric field around the sensory nerves, conduction in the C- and A-delta fibers is reduced.

In conclusion, we reported 3 patients with occipital neuralgia resistant to conventional therapy, who showed a strong positive effect of PRF on the occipital nerves. Several limitations need to be acknowledged. First, each outcome measure is subjective and dependent on personal interpretation, which limits the objectivity of the study. In addition, the small sample sizes of the published studies limit the power of the reported findings. Moreover, to date, no randomized controlled trials have been conducted in patients with occipital neuralgia [13]. Although further studies involving larger number of participants with occipital neuralgia are still needed, our initial observations showed that PRF in the occipital nerves may be an effective therapeutic option for the control of refractory occipital neuralgia.

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COMPLIANCE WITH ETHICAL STANDARDS:

- The authors declare that they have no conflict of interest.
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A RELAPSE OF "RECURRENT PAINFUL OPHTHALMOPLEGIC NEUROPATHY" AFTER COVID-19 VACCINATION, CASE REPORT AND REVIEW OF THE LITERATURE.

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ABSTRACT

The purpose of this paper is to describe the first case report of a relapse of "Recurrent Painful Ophthalmoplegic Neuropathy" (RPON), formerly known as "Ophthalmoplegic Migraine", after COVID-19 immunization. RPON is a rare form of neuropathy characterized by repeated attacks of paresis of one or more ocular cranial nerves with ipsilateral headache. While headache and ocular cranial nerve palsies alone have been described after vaccination, especially after COVID-19 immunization, there are only minimal reports of RPON in ***children***, or painful ocular cranial nerve palsies in the ***adult*** population. We hereby present the first case report of a patient with RPON, who had a recurrence after the 3rd dose of the BNT162b2 mRNA vaccine against SARS-Cov-2. In addition, as far we know, this case is also the first case report of a relapse of known RPON after immunization in the ***adult*** population. The rarity of these cases may be explained by the fact, that since recently adult vaccination was not so common, and RPON is also a rare entity. In our opinion, this article will add important insights not only to the field of COVID-19 vaccination, but also to the field investigating the pathogenesis of RPON. This paper comes to strengthen the current opinion, that RPON is actually a neuropathy, while headache could be a secondary event that takes place in some individuals whose anatomy and physiology endeavour the earlier triggering of an ipsilateral headache.

KEY-WORDS: COVID-19, vaccination, headache, ophthalmoplegic migraine, cranial neuropathy.

ΥΠΟΤΡΟΠΗ «ΕΠΑΝΑΛΑΜΒΑΝΟΜΕΝΗΣ ΕΠΩΔΥΝΗΣ ΟΦΘΑΛΜΟΠΛΗΓΙΚΗΣ ΝΕΥΡΟΠΑΘΕΙΑΣ» ΕΠΕΙΤΑ ΑΠΟ COVID-19 ΕΜΒΟΛΙΑΣΜΟ, ΑΝΑΦΟΡΑ ΠΕΡΙΠΤΩΣΕΩΣ ΚΑΙ ΑΝΑΣΚΟΠΗΣΗ ΤΗΣ ΒΙΒΛΙΟΓΡΑΦΙΑΣ.

Μαρία Λίμα, Βάιος Σαμαράς, Δημήτριος Παρίσης, Νικόλαος Γρηγοριάδης, Παναγιώτης Ιωαννίδης.

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ΠΕΡΙΛΗΨΗ

Ο σκοπός αυτού του άρθρου είναι η περιγραφή της πρώτης περίπτωσης εμφάνισης υποτροπής «Επαναλαμβανόμενης Επώδυνης Οφθαλμοπληγικής Νευροπάθειας» (ΕΕΟΝ), πρωτύτερα γνωστή ως «Οφθαλμοπληγική Ημικρανία», έπειτα από COVID-19 εμβολιασμό. Η ΕΕΟΝ είναι μία σπάνια μορφή νευροπάθειας που χαρακτηρίζεται από επαναλαμβανόμενες προσβολές πάρεσης ενός ή περισσότερων κρανιακών νεύρων με σύστοιχη κεφαλαλγία. Παρότι έχουν αναφερθεί περιστατικά κεφαλαλγίας ή πάρεσης κρανιακών νεύρων ξεχωριστά έπειτα από εμβολιασμό, ειδικά έπειτα από COVID-19 εμβολιασμό, υπάρχουν μόνο ελάχιστες αναφορές εμφάνισης ΕΕΟΝ ***σε παιδιά,*** ή «επώδυνης οφθαλμοπάρεσης» σε ***ενήλικες.*** Στο παρόν άρθρο περιγράφουμε το πρώτο γνωστό περιστατικό ασθενούς με ιστορικό ΕΕΟΝ, ο οποίος εμφάνισε υποτροπή έπειτα από την 3η δόση εμβολιασμού με το BNT162b2 mRNA εμβόλιο έναντι του κωρονοϊού (SARS-CoV-2). Επιπλέον, εξ όσων γνωρίζουμε, αυτή η περίπτωση είναι επίσης η πρώτη αναφορά υποτροπής γνωστής ΕΕΟΝ έπειτα από εμβολιασμό σε ***ενήλικο*** πληθυσμό. Η σπανιότητα αυτών των αναφορών εξηγείται από το γεγονός ότι μέχρι πρόσφατα ο εμβολιασμός ενηλικών δεν ήταν συνήθης, και η ΕΕΟΝ είναι επίσης μία σπάνια οντότητα. Κατά την γνώμη μας, το άρθρο αυτό θα προσθέσει σημαντική γνώση όχι μόνο στον τομέα μελέτης του

COVID-19 εμβολιασμού, αλλά ιδίως στον τομέα μελέτης της παθογένεσης της ΕΕΟΝ. Το άρθρο αυτό έρχεται να ισχυροποιήσει την τρέχουσα αντίληψη, ότι η ΕΕΟΝ είναι όντως νευροπάθεια, ενώ η κεφαλαλγία που την συνοδεύει θα μπορούσε να είναι ένα δευτερογενές γεγονός που λαμβάνει χώρα σε ορισμένα άτομα των οποίων η ανατομία και φυσιολογία ευνοούν την πρωθύστερη ενεργοποίηση μιας σύστοιχης κεφαλαλγίας.

ΛΕΞΕΙΣ ΚΛΕΙΔΙΑ: COVID-19, εμβολιασμός, κεφαλαλγία, οφθαλμοπληγική ημικρανία, κρανιακή νευροπάθεια.

INTRODUCTION

According to the International Classification of Headache Disorders 3rd edition 2018 (ICHD3) (code 13.10), "Recurrent Painful Ophthalmoplegic Neuropathy" (RPON), formerly known as "Ophthalmoplegic Migraine" (OM), is characterized as: "Repeated attacks of paresis of one or more ocular cranial nerves (CN), commonly the third (IIIrd) CN, with ipsilateral headache".[1] The exact pathogenesis of the syndrome remains unclarified, while it may also not be the same in all cases. The only radiological finding that can be demonstrated using MRI, is thickening or enhancement of the IIIrd CN at its exit from the midbrain. [1] Moreover, taking into consideration the "relapsing-remitting" pattern of the syndrome and good response to corticosteroids, the disorder is in accordance with the current view that it is an inflammatory or demyelinating neuropathy. [2] This process on the nerve could in turn affect trigeminal fibers and activate a trigeminovascular response, which causes ipsilateral headache. [2,3]

Already since 1949, Rosen supported that ocular and neuro-ocular manifestations are not a rare post-vaccinal complication. [4] There are many cases of post-vaccinal cranial neuropathies, ocular cranial nerve palsies (OCNP) included, some of them with a recurrent pattern. Many similar cases have also been described after COVID-19 immunization, where VIth CN palsy is the most common among OCNP. [5]Some of these cases are summarized in the table below (table 1).

Table 1. OCNP after immunization, especially after COVID-19 vaccination, and after COVID-19 infection.

1. Post-vaccinal OCNP	Rosen, 1948 (DOI:10.1016/S0002-9394(48)91808-X)	R×os, Mart×n, & Mercadal, 2014 (DOI:10.1016/j.anpedi.2014.02.010)	Essrani, Essrani, Mehershahi, Lohana, & Sudhakaran, 2018 (DOI:10.7759/cureus.3759)	Kim et al., 2021 (DOI:10.1159/000511025)
2. Post-vaccinal OCNP with a recurrent pattern	Werner, Savino, & Schatz, 1983 (DOI:10.1001/archopht.1983.01040010607016)	McCormick, Dinakaran, Bhola, & Rennie, 2001 (DOI:10.1038/eye.2001.122)	Leiderman, Lessell, & Cestari, 2009 (DOI:10.1016/j.jaapos.2008.12.137)	
3. Post-vaccinal OCNP after COVID-19 immunization	Kubota, Hasegawa, Ikeda, & Aoki, 2021 (DOI:10.12688/f1000research.74299.2)	Reyes-Capo, Stevens, & Cavuoto, 2021 (DOI:10.1016/j.jaapos.2021.05.003)	Cicalese et al., 2022 (DOI:10.1136/bcr-2021-246485)	Kerbage, Haddad, & Haddad, 2022 (DOI:10.1177/2050313x221074454)
	Khalili, Khorrami, & Jahanbani-Ardakani, 2022 (DOI:10.1016/j.jfo.2022.03.001)	Veisi, Najafi, Hassanpour, & Bagheri, 2022 (DOI:10.1080/01658107.2022.2032204)	Lotan, Lydston, & Levy, 2022 (DOI:10.1097/wno.0000000000001537) *(systematic review)*	Dutta et al., 2022 (DOI:10.7759/cureus.21376) *(adverse effects reports in VigiBase)*
4. OCNP after COVID-19 infection	Faucher, Rey, Aguadisch, & Degos, 2020 (DOI:10.1007/s00415-020-09987-x)	Pascual-Go×i et al., 2020 (DOI:10.1212/nxi.0000000000000823)	Wei, Yin, Huang, & Guo, 2020 (DOI:10.1007/s00415-020-09773-9)	Fitzpatrick et al., 2021 (DOI:10.1097/wno.0000000000001160)

However, according to the research of the literature that we have conducted, there are only a few cases of post-vaccinal attack of RPON or painful OCNP. Chan et al. described a case of a 17-month-old, who developed an isolated IIIrd CN palsy two weeks after measles immunization [6]. Later, the boy developed same episodes with headache, that were finally characterized as OM (RPON). [7] Another very interesting case is the story of a 9-year-old boy, who developed three attacks of IIIrd CN palsy with headache, each of them 10 days after the injection of a triple vaccine. [3] As regards the adult population, there is a case of painful IIIrd CN palsy in a 79-year-old man after influenza vaccination, [8] and a report of VIth CN palsy with throbbing occipital headache two days after the 2nd dose of COVID-19 vaccination, with the ChAdOx1/AD1222 vaccine, but in that case the patient was also febrile.[9] However, we could not find any case of ***relapse*** of known RPON after vaccination in the ***adult*** population. The results are summarized in table 2.

Table 2. Post-vaccinal RPON or *painful* OCNP

Chan, Sogg et al. 1980 (DOI:10.1016/0002-9394(80)90019-7)	Hassin 1987 (DOI:10.1016/0002-9394(87)90020-1)	Lance and Zagami 2001 (DOI:10.1046/j.1468-2982.2001.00160.x)	de Almeida, Teodoro et al. 2011 (DOI:10.5402/2011/849757)	Basnet, Bhandari et al. 2022 (DOI:10.1016/j.amsu.2022.104434)

CASE DISCRIPTION

Hereby, we present a case of a 65-year-old man, who had been diagnosed earlier in our clinic with RPON, and this time came with another attack, 10 days after the 3rd dose of the BNT162b2 COVID-19 mRNA vaccine.

The patient suffered from migraine type headaches since childhood, usually right periocular throbbing headache, with nausea, photophobia and echophobia. Later on his life the episodes were accompanied by diplopia, due to oculomotor nerve palsy, and for these episodes he had been investigated in our department. Paraclinical investigation with laboratory, immunological, imaging examination (including brain MRI and chest CT), antibodies for myasthenia, electromyography, and lumbar puncture (cytochemistry, oligoclonal bands in serum and cerebrospinal fluid), did not reveal any underlying structural, vascular, ischemic, inflammatory or demyelinating pathology. The patient is under medication for hypertension, which is well-controlled, without any other vascular risk factors. From his family history, his mother was also suffering from headaches. According to the International Classification of Headache Disorders 3rd edition 2018 (ICHD3) (code 13.10) the patient fulfills the criteria of RPON (1).

This time, the patient had another relapse of RPON, only 10 days after a booster dose of COVID-19 mRNA immunization. He presented to our clinic with right periorbital throbbing headache, as well as corresponding blepharoptosis and diplopia 2 days later. The neurological examination revealed a right IIIrd CN palsy, with blepharoptosis, eye in abduction and downward turn, pupils with mild right supremacy, with preservation of the photomotor reflex, and diplopia, without other neurological symptoms or signs. We performed another thorough investigation, with laboratory, immunological, imaging examination (Brain CT, CT-Angiography, CT-Venography, Brain MRI) and lumbar puncture (cytochemistry, oligoclonal bands in serum and cerebrospinal fluid), which again did not reveal any underlying structural, vascular, ischemic, inflammatory or demyelinating pathology. The patient was treated with corticosteroids in the acute and subacute phase and oculomotor palsy gradually resolved within three months.

DISCUSSION

According to the algorithm of World Health Organization (WHO) for the assessment of the causality of Adverse Events Following Immunization (AEFI), [10] we could classify our case in the category of ***"consistent causal association to immunization"***. First of all, a possible causal association of OCNP and RPON with vaccination has been described and can be explained, accepting the current view, that RPON is more of neuropathy (inflammatory or demyelinating in nature) rather than migraine. Moreover as regards SARS-CoV-2, it is known that it can enter the Central Nervous System (CNS) and cause neurological manifestations, [11] while in addition it may have a strong link with demyelination in the CNS. [12] In particular, cases of OCNP have been described after COVID-19 infection (table 1.4). Consequently, a possible mechanism of oculomotor nerve palsy after COVID-19 vaccination could be a similar triggering of a misdirected immune response against myelin sheaths and surrounding axons, as in COVID-19 infection, for example via antigenic mimicry, bystander activation, or "superantigens" mechanism. [12,13] As we have already mentioned above, OCNP after COVID-19 vaccination have been actually described, while RPON could be described as a Painful OCNP.

The next steps of AEFI algorithm are also met. We have excluded any other possible explanation for the condition of our patient, while until now there is not such kind of data that would ***reject*** a potential

causal association.[13] It is worth noting the necessity of lumbar puncture to rule out other conditions, such as infectious, inflammatory, or neoplastic processes, especially in the first episode of RPON, where results should be normal.[14] Possibly inflammatory CSF findings have been described in only two cases, one case with a single oligoclonal band, and another with an elevated IgG index, both, however, involving the fourth nerve, raising the question of a possible different etiologically form of RPON.[15] A case of increased CMV IgG levels in CSF, is of doubtful significance, since it is a common finding in general population.[16] Proceeding to the reasoning of the AEFI algorithm, neurologic symptoms and signs 9-11 days after vaccination can be considered as post-vaccinal,[4] while similar previous cases of RPON after immunization, have been surprisingly described also around 10 days after vaccination.[3,4] Finally, the booster vaccine dose was more commonly associated with headache, and CN palsies have been also described after a booster dose,[17] which is in accordance with the mechanisms of adaptive immunity, that takes some days or weeks to develop, while for example some cytokines achieve higher titers after the 2nd vaccine dose.[18] Our patient developed the episode of RPON after a booster vaccine dose, which is compatible with this theory.

In conclusion, it is important to highlight the possible trigger factors of RPON, in order to better understand its pathogenesis, which still remains unclarified. Taking into consideration this case and similar other cases of cranial and OCNP after vaccination, we may accept with more certainty, that the core problem of RPON is a neuropathy, while headache could be a secondary event that takes place in some individuals whose anatomical structures and physiology endeavour the earlier triggering of an ipsilateral headache. For this reason, we believe that this case report, is important not only because it is the first case report that describes a clear recurrence of RPON after COVID-19 vaccination, but also because it is the first report of relapse of RPON after immunization, and especially with an mRNA vaccine, ***in the adult population***, adding valuable information into the pathophysiology of the syndrome and secondary to the study field of COVID-19 infection, COVID-19 vaccines and their potential side effects. The rarity of these cases in adults can be explained by the fact, that since recently adult vaccination was not common, and RPON is also a rare entity. However, neurologists should be aware of this and similar potential side effects of COVID-19 vaccination, and vaccines in general, which in no case outweigh their life-saving benefits, in order to act properly. According to ICHD-3, "treatment with corticosteroids is beneficial in some patients" and is actually the common practice.[1] In a literature review, 96.2% of patients who received corticosteroids alone, benefited from the therapy. A benefit from Non-Steroid Anti-inflammatory Drugs, like indomethacin, and anti-migraine medicine, has also been described in the past. [2] Although RPON is also considered a self-limiting condition, that can be improved up to a couple of months later, there are patients prone to recurrent episodes with persistent eye misalignment, where injection of botulinum toxin or strabismus surgery may be considered.[19]

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COMPLIANCE WITH ETHICAL STANDARDS:

- The authors declare that they have no conflict of interest.
- Funding: None.
- Consent to publish: The patient has consented to the submission of the case report to the journal.

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Το περιοδικό *ΑΡΧΕΙΑ ΚΛΙΝΙΚΗΣ ΝΕΥΡΟΛΟΓΙΑΣ* κυκλοφορεί κάθε δύο μήνες και αποτελεί το επίσημο όργανο της Ελληνικής Νευρολογικής Εταιρείας. Με την Υπουργική Απόφαση ΔΥ2α/Γ.Π.οικ. 66198/1/6/2006, που δημοσιεύθηκε στο Φ.Ε.Κ. 1034/Β/1-08-2006, προστέθηκε στον κατάλογο των περιοδικών με Εθνική Αναγνώριση.

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Δομή της ύλης

Γίνονται δεκτές εργασίες στα ελληνικά ή αγγλικά.
Υποβάλλεται πάντοτε ο τίτλος, τα ονόματα των συγγραφέων και η περίληψη και στα αγγλικά.
Τα κείμενα θα πρέπει να αποστέλλονται σε μορφή Microsoft Word document.
Σελίδα τίτλου: Περιέχει τον τίτλο, τα πλήρη ονόματα των συγγραφέων, το ίδρυμα προέλευσης, τη διεύθυνση και το τηλέφωνο του υπευθύνου για την αλληλογραφία και τον καταμετρημένο αριθμό λέξεων.
Περίληψη: Παρουσιάζει τα κυριότερα σημεία της εργασίας. Δεν πρέπει να υπερβαίνει τις 250 λέξεις. Στο τέλος της παρατίθενται 3-10 λέξεις ευρετηρίου.
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Εικόνες: Αποστέλλονται τα πρωτότυπα σχέδια ή φωτογραφίες καλής ποιότητας. Να υποβάλλονται σαν αρχεία εικόνας ξεχωριστά από το κείμενο του MS Word. Αριθμούνται με τη σειρά εμφάνισης στο κείμενο. Στο κείμενο θα πρέπει να υπάρχει σαφής παραπομπή στον τίτλο των ηλεκτρονικών αρχείων. Σε ξεχωριστή σελίδα αναγράφονται οι τίτλοι των εικόνων και οι τυχόν επεξηγήσεις.
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Θα πρέπει να συμπληρωθούν ΟΛΑ τα σημεία του εντύπου. Άλλη συνοδευτική επιστολή δεν είναι απαραίτητη.

Είδος άρθρου (σημειώστε μόνο ένα)

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❑ Βραχεία ανασκόπηση ❑ Ειδικό άρθρο ❑ Γράμμα στη σύνταξη ❑ Νευρο-εικόνες

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- ❑ Δομημένη περίληψη στα Ελληνικά και στα Αγγλικά
- ❑ Έως πέντε λέξεις ευρετηριασμού *(κατά προτίμηση από το MeSH Hellas-Βιοϊατρική Ορολογία)* στα Ελληνικά και στα Αγγλικά
- ❑ Όλα τα ονόματα των συγγραφέων στις βιβλιογραφικές παραπομπές (*μέχρι 6 και στη συνέχεια* «*και συν.*» *ή* «*et al*»)
- ❑ Η βιβλιογραφία στις τελευταίες σελίδες των άρθρων

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Δηλώνω υπεύθυνα ότι:

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4. Δεν υπάρχουν θέματα σύγκρουσης συμφερόντων – σε περίπτωση εξωτερικής χρηματοδότησης αυτό θα πρέπει να αναφέρεται στο τέλος της εργασίας.

Ο υπεύθυνος για την αλληλογραφία συγγραφέας

(υπογραφή)