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Neuromodulation in the Management of Allergic Chronic Vaginitis

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Abstract

Chronic vaginitis (CV) affects 16% of women. While a number of distinct diagnoses account for the underlying causes of CV, allergic inflammation is also present in a significant number of cases and may range from 25 to 54% of CV patients. Allergic inflammation in CV is encountered as a result of: i) direct sensitization of the vaginal mucosa to latex, local products, Candida, bacteria, etc.; ii) inhalant allergy compounding the chronic vaginitis syndrome; iii) immune cell activation secondary to neurogenic inflammation in the context of chronic neuropathic pain. Despite the varying nature of specific neuro-immune interactions, chronic pain/irritation remains a cardinal feature of CV which needs to be addressed as a priority independently of specific gynecological or allergy-modifying interventions. This is necessary not only for reasons of symptom relief but also because long-term neuronal changes due to inflammation and chronic pain have a profound effect on the course of CV by potentiating adverse pro-inflammatory and degenerating processes. The pathophysiology of these processes and their alteration by means of neuromodulators is presented with a view of long-term control of chronic pain and neurogenic inflammation. Special emphasis is placed on gamma-aminobutyric acid-served pathways, the use of tricyclic antidepressants, serotonin-reuptake inhibitors and certain antihistamines with anti-serotoninergic properties.

Keywords: Chronic vaginitis; Allergy; Immunotherapy; Inflammation; Neuropathic pain

Introduction

Chronic vaginitis (CV), unrelated to infection or trauma, is common in the general population and is one of the most frequent reasons for visits to gynecologists. Chronic vulvar and vaginal complaints are known to be under-reported and under-diagnosed. It is estimated that at least 16% of women will experience chronic vaginal and/or vulvar pain for at least three to six months, which is the clinical definition of vulvodynia [1]. For chronic pruritus, dysesthesia, paresthesia or other types of discomfort there are no valid data. The term CV represents a multifactorial and highly heterogeneous condition, which may result from several distinct conditions or their combination [2,3]. Allergies often co-exist with CV. It is estimated that 25-54% of women with CV carry either a current diagnosis or a past history of at least one allergic disease clinical manifestation [2]. The concurrence of allergy and CV exceeds the expected rates. The prevalence of atopic diathesis in the general population, that is, the natural ability to mount an IgE response and exhibit immediate type skin sensitivity to allergens is assessed as 50%. However, manifestation of allergic diseases in the general population occurs at significantly lower rates than those reported in the CV-affected segment of the population. Expected rates for allergic disease in the general population are generally reported as 10-20% for allergic rhinitis and 5-7% for asthma, and the one-time incidence of chronic urticaria may be up to 20% [4]. While pre-existing atopic disposition to mount IgE responses to allergens represents a potential for the development of allergic sensitization, it does not necessarily lead to clinical expression. Compared to the general population, the prevalence of atopic diathesis appears to be nearly equal to the presence of clinical allergy among women with CV.

Allergic sensitization to Candida as well as successful treatment of recurrent vulvovaginal candidiasis with Candida immunotherapy has been described [5,6]. Sensitization to latex and to a variety of local medications and other products has also been presented along with a variety of contact-type sensitizations [7].

In addition to locally presented and locally acting sensitizers, a clinically significant association between CV and allergic airway responses to inhalants has also been established and specific mechanisms to explain this association have been proposed [8,9]. Additionally, selection criteria for CV patients likely to benefit from allergen immunotherapy have been identified and the long-term outcome of such selection has been assessed as favorable [10]. In general, CV patients presenting with somatic type responses, that is, surface symptoms dominated by pruritus or other mucosal or skin irritation, but not deep visceral pain, tend to respond earlier to allergen immunotherapy, require fewer courses of antibiotics and antifungals, and are often able to stop their long-term pain-control medication. These patients tend to suffer primarily from recurrent vulvovaginal candidiasis symptoms, although no more than 32% of allergic CV patients with recurrent vulvovaginal candidiasis demonstrated evidence of *Candida* sensitization [10]. Alternatively, allergen immunotherapy has been less rewarding for patients with visceral type pain or neuropathic pain. Furthermore, the vast majority of CV patients who present with either visceral or neuropathic pain remain on long-term pain control regimens 3-5 years into allergen immunotherapy. The gynecological diagnoses in this second category

vary widely and include (in order of frequency) vestibulodynia, recurrent vulvovaginal candidiasis, bacterial vaginosis, contact dermatitis, lichen simplex, lichen sclerosus and desquamative inflammatory vaginitis, and can appear in combinations [10]. Neither the kinds of allergens nor the diagnoses of allergic diseases appear to be specific to the "pruritic" versus "deep pain" groups or when allergic CV is compared to the general population allergies [10]. It is for this reasons that chronic pain in CV is discussed as a result of inflammation as well as an independent factor likely to lead to:

- Perpetuation of CV in spite of specific gynecological treatment,
- Chronic ill health,
- Chronic immunological changes which hinder the immune modification intended by immunotherapy.

Effective pain management in CV is viewed not only as symptom control but also as a primary therapeutic objective

Pro-inflammatory cytokines and gamma-aminobutyric acid-dependent responses

It has been long recognized that gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the central nervous system. It reduces nerve excitability by suppressing calcium ion influx into the cytoplasm. It allows influx of negatively charged chloride ions and outflow of positively charged potassium ions [11]. These actions result in hyperpolarization of the nerve cell membrane. The relevance of GABA to chronic pain is due to its function in the hypothalamus and hippocampus where it exerts a suppressive action on pain through specific GABAergic receptors. Exogenous GABA does not cross the blood-brain barrier [12]. Exogenous administration of GABA results in clinical responses only because of its absorption from the periventricular nucleus (PVN), a thin sheet of neurons in the wall of the third ventricle which is part of a composite structure of the hypothalamus. The PVN has no blood-brain barrier [13]. In addition to its significance in the delivery and absorption of drugs, it is also an important gate-like station in the central processing of pain/analgesia. The caudal area is known to have a major role in the regulation of sympathetic outflow and is regarded as the "rage center." Also, the PVN is the site of major regulatory action regarding glucocorticoid responses to stress. In this way the PVN represents both a port of entry and a major target of GABAergic modification.

The effects of GABA on the central nervous system, endocrine organs, bone marrow and immune cells are manifold and are yet to be fully delineated. One remarkable property of GABA is its promotion of the catabolism of serotonin to N-acetyl-serotonin, a precursor of melatonin [14]. In addition to direct effects on the induction, length and quality of sleep, it is important in the reduction of serotonin activity, an important component in the management of CV and a factor to be considered vis-à-vis the use of serotonin reuptake inhibitors.

A number of other important effects of GABA activity have been recognized, which are relevant to the management of chronic pain. Notable is the ability of GABA to increase the production of the neuropeptide Y, a neurotransmitter involved in neurogenic inflammation and also known to up-regulate the expression of glucocorticoid receptors [15]. A remarkable finding is the existence of an excitatory GABA-dependent mechanism whose efferent end is the airway epithelium and which appears to be operative in asthma [16]. While the full significance of this observation remains to be assessed, some authors have noted that, in spite of the high prevalence of allergy in general in CV, the prevalence of asthma among patients with allergic CV is quite low [8,10].

The pharmacology of GABAergic activity is expanding. Traditionally, drugs are categorized based on the type of GABA receptor involved in their action, but this area is expanding too. $GABA_A$ agonists include barbiturates, benzodiazepines, propofol and ethanol. $GABA_B$ agonists include, among others, baclofen, a skeletal muscle relaxant often used in the management of vulvodynia including CV symptoms, and, notoriously, γ-hydroxy-butyric acid, a precursor of GABA and also a "date-rape" drug. Research in the area of GABA reuptake inhibitors is growing as well. GABA-transaminase inhibitors famously include valproate and vigabatrin, both of which have been used in vulvodynia including CV as well as in other forms of chronic pain with a neuropathic component. The main stay of long-term management of GABA-dependent activity in vulvodynia including CV are the GABA analogues gabapentin and pregabalin.

While the efferent effect of impaired GABA activity is yet to be studied (i.e., increased sympathetic outflow through the PVN, neuropeptide production contributing to peripheral neurogenic inflammation, epithelial GABA-dependent inflammatory activity, effects of GABA on stem cells, effects on resident immune cells, etc.) it is the afferent direction of inflammatory responses and their effect on GABA production which constitutes a therapeutic priority. In this context, gabapentin, pregabalin, benzodiazepines, vigabatrin, valproate and barbiturates, as well as muscle relaxants such as baclofen, are used to control symptoms triggered and sustained by ongoing peripheral inflammation as well as enhance central GABAergic activity with the expectation of suppressing neurogenic inflammation. Evidence to support this approach is abundant and its full review is beyond the scope of the present study. Virtually every major pro-inflammatory cytokine has been incriminated in suppressing or opposing GABAergic neurotransmission.

Interleukin-1 (IL-1), a strong pro-inflammatory cytokine, is known to increase calcium influx (and thus promote nerve cell membrane depolarization) in hippocampal slice preparations [17]. In higher concentrations (picomolar) IL-1 increases cytoplasmic calcium ions in primary cultures of rat hypothalamic neurons [18]. Since the neurons responding to IL-1 under these circumstances exhibit strong GABAergic activity, long-term use of GABA agonists/analogues/reuptake inhibitors or GABA-transaminase inhibitors opposes these effects which are conducive to the perpetuation of chronic pain.

Interleukin-6 (IL-6) can profoundly affect the ability of the hippocampus to maintain long-term potentiation, a critical physiological process involved in memory consolidation [19]. IL-1β seems to be involved in the same process as evidenced by experiments utilizing injected lipopolysaccharide antigen to precipitate a steady status of chronic inflammation [20]. Most impressively, in transgenic mice whose astrocytes had been manipulated to chronically overproduce IL-6, hippocampal neurogenesis was found to have decreased by 63% [21]. Disrupted synaptic plasticity is also supported by these findings [19-21]. In this context, the management of chronic pain in allergic CV, as well as in other similar disorders, may graduate from a chronic inflammatory disease to that of mental health with long-term effects dominated by a degenerative pathology.

Of all pro-inflammatory cytokines, the one that has received the most attention is Tumor Necrosis Factor-α (TNF-α). The effects of TNF-α on the precipitation and sustainment of fever, septic responses, acute phase reactions, hepatic responses, mucosal inflammation,

chronic pain, malaise, insomnia, fatigue and other conditions are well recognized [22]. Interest in the actions of TNF-α and their modification keeps growing and parallels the availability of biologics targeting the TNF-α. Literature presenting the detrimental effects of unregulated TNF-α and the benefits of TNF-α suppression is enormous. Regarding CV, there is evidence of an inherited disorder resulting in a polymorphism of the TNF-α promoter region which renders women prone to bacterial vaginosis, an important factor to consider in the evaluation and management of allergic CV [23]. This observation is quite weighty in view of the exceptionally poor response of allergy-complicated bacterial vaginosis to allergen-specific immunotherapy [10]. Given the mapping of the TNF gene to an area of the chromosome 6 which is heavily involved with identity recognition and immune response, it is expected that in the near future research regarding TNF-dependent susceptibility to infection and sustained chronic inflammation (which may involve the kind of manifold manifestations of contiguous gene syndromes as well as highly refined gene-gene interactions) will be expanded. In terms of immediate practical significance, TNF-α is uniquely interesting cytokine in the management of chronic pain: not only does TNF-α suppress GABAergic activity but, in a remarkable paradigm of successfully modified neurogenic inflammation, enhanced GABAergic activity has been shown to suppress inflammation mediated by TNF-α [24].

Neurotransmitter reuptake inhibition

Antidepressants have been established as standards treatment for chronic pain. A recent meta-analysis of 229 studies on chronic neuropathic pain resulted in strong recommendations as first line treatment for tricyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and GABA analogues. The options of TCA and tramadol monotherapy were characterized by low cost. Weak recommendations were made for opioids and for local agents such as lidocaine, capsaicin and botulinum toxin A [25]. Before the 1990s TCAs were the mainstay of treatment for depression. They all have similar effects and side effects as well as mechanism of action. They block the reuptake of norepinephrine and serotonin, and to a lesser extent, dopamine. Their side effects are derived from blockade of muscarinic cholinergic receptors, H1 histamine receptors and alpha-1-adrenergic receptors [26,27]. The primary target of TCAs is to block the reuptake of norepinephrine. Clomipramine, however, also has a high affinity for serotonin receptors which sets it apart from other TCAs. Its active metabolite, N-desmethylclomipramine, is a potent norepinephrine reuptake inhibitor. Clomipramine may be perceived as an evolutionary link between the original TCA and the selective serotonin reuptake inhibitors (SSRI).

Low dose nortriptyline has proved effective in controlling neuropathic pain and is considered a safe choice especially among patients with absorption, metabolism and compliance problems. It is the first choice among TCA for three reasons: it shows the least anticholinergic activity, it is the least likely to cause significant orthostatic hypotension, and has an established therapeutic range which can be safely assessed by its serum levels. The pharmacokinetics of nortriptyline show a noteworthy dose-response curve that takes the form of an inverted U. Practically, this means that, at serum nortriptyline levels exceeding 150 ng/mL, decreasing the dose may result in increased response [28]. The major concern with all TCAs is the risk for overdose-related toxicity. Conduction block, ventricular tachycardia and fibrillation are recognized complications [28].

The advent of SSRIs has provided the clinician with a class of drugs which are easier to prescribe as they are less sedating, less likely to cause weight gain, have lesser anticholinergic activity, and if overdosed, are less likely to lead to fatalities as compared to TCAs. They have a slow onset, and 3 to 6 weeks often pass before noticeable responses. Sertraline, paroxetine, fluoxetine, citalopram and escitalopram are all used in the management of pain in CV. Paroxetine is the least preferred agent as it is the SSRI which is most frequently associated with sedation, weight gain and sexual dysfunction [28]. In the authors' experience, escitalopram and fluoxetine have proved quite satisfactory. Fatigue, headaches, sexual dysfunction, as well as sleep disturbance are reported as side effects but usually abate after 2-4 weeks of treatment. Doses are to be gradually increased. Of all side effects, sexual dysfunction is the one which is most obviously dose-related [28].

Duloxetine and venlafaxine, the two major SNRIs, have safety and side-effect profiles similar to those of SSRIs but may be more efficient than SSRIs in controlling neuropathic pain [28,29]. In high doses, SNRIs may cause hypertension.

Other agents affecting levels of neurotransmitters are bupropion, mirtazapine, trazodone and nefazodone, and will be discussed as second-line or add-on choices. Monoamine oxidase inhibitors are rarely used because of their interactions and risk for hypertensive crises.

It should be stated here that no single abnormality in any of the neurotransmitters or their receptors has been demonstrated to be responsible for chronic neuropathic pain or for neurogenic inflammation. Currently, chronic pain is believed to result from the complex interaction of infection, inflammation, previous traumas, genetic factors and other conditions. The impact of medications which affect the level of neurotransmitters is highly individualized. This limitation in the current level of knowledge is exemplified by the use of SSRIs or SNRIs in conjunction with GABA analogues, a choice which, at least as far as serotonin availability is concerned, appears to be contradictory since the earlier increase and the latter decrease serotonin levels. In practice, however, this combination is not uncommon and frequently proves rewarding. Safety data addressing this issue and supporting the combination of GABA analogues with SSRIs/SNRIs have been published [30].

In recalcitrant cases, combinations of neuromodulators may be considered. The leading concern in this respect is the risk for serotonin syndrome. Serotonin syndrome is a potentially life-threatening condition and typically occurs when two or more serotoninergic agents are given concurrently or before adequate washout. Such combinations may involve any of the SSRIs/SNRIs, monoamine oxidase inhibitors and TCAs, as well as a number of drugs which may not have an antidepressant profile but increase serotonin levels such as tramadol, triptans and cocaine [31]. Serotonin syndrome is characterized by extreme gastrointestinal symptoms, altered mental status, ataxia, increased reflexes and profound autonomic alterations (hyperthermia, hypertension, tachycardia, diaphoresis), and its manifestations may overlap with those of hypertensive crises which often complicate the use of monoamine oxidase inhibitors. Benzodiazepines and cyproheptadine have both been reported as effective modalities in the management of the serotonin syndrome; an observation which reinforces the hypothesis of an anti-serotoninergic effect of cyproheptadine [31].

Augmentation therapy employing the addition of a second neuromodulator is a standard approach in the management of

depression but little is known about this approach in the management of CV. Frequently employed add-on choices include the following:

Bupropion is often added to an SSRI/SNRI and is also safely added to TCAs or to mirtazapine. It has a good record in the management of fatigue which frequently develops in the context of CV-related chronic pain [28]. It also provides a reasonable alternative when sexual dysfunction is involved since this complaint is likely to worsen with increasing doses of SSRIs/SNRIs.

Buspirone is a rather weak agent which by itself is unlikely to control the chronic pain of CV. It can however be safely used with SSRIs/SNRIs as well as with TCAs. Doses can be titrated against symptoms and may be limited by side effects such as dizziness, nausea and sedation.

Trazodone, a serotonin antagonist reuptake inhibitor (SARI), is another effective choice when augmentation is needed. Its addition to an SSRI/SNRI is a common strategy in the management of depression especially when insomnia needs to be treated.

Mirtazapine is often used as monotherapy but can routinely be added to SSRIs/SNRIs and bupropion [28].

While all these options are available and their efficacy has been demonstrated, their impact on inflammation remains unclear. Unlike GABA analogues and GABAergic modification in general, the effect that antidepressants have on pro-inflammatory cytokines is poorly understood. In a recent study of children and adolescents with depression and/or anxiety, TNF-α declined as a result of treatment with fluoxetine for 8 weeks, but IL-6 and IL-1β did not. Furthermore, patients who, before treatment with fluoxetine, had high levels of all three of the measured pro-inflammatory cytokines showed no clinical improvement with fluoxetine treatment [32]. It is possible that an SSRI-responsive versus an SSRI-nonresponsive subpopulation may be discernible and this differentiation may have an impact on management. The designation, however, of "depression and/or anxiety" may need to be addressed again as the two disorders are quite distinct and may by themselves account for the observed differences in clinical response and baseline cytokine levels (i.e., the pre-existing high levels of TNF-α might have been more prevalent and/or constitutionally higher in the depressed subpopulation). In fact, in the routine practice of allergy, the clinical characteristics of the depressed versus anxious patient are quite prominent and would definitely weigh towards different treatment options, the predominantly anxious patient being more likely to respond to GABAergic modulation, while the depressed patient would primarily require treatment with a neurotransmitter reuptake inhibitor. Other studies have clearly demonstrated a decline in IL-6 in depressed patients treated with sertraline; a neuroprotective effect of trazodone through inhibition of NF-κB and other pro-inflammatory mediators; and suppression of TNF-α in the cerebrospinal fluid of hydroxydopamine-lesioned animals following treatment with a combination of fluoxetine and buspirone [33-35]. In general, the evidence of favorable immune modulation in the direction of suppressing pro-inflammatory cytokines by means of neurotransmitter reuptake inhibition is mounting although clear anatomic descriptions, histological data, mechanisms of action and a comprehensive theoretical model are still lacking.

Cholinergic modulation of inflammation

Pavlov and Tracey described a "cholinergic anti-inflammatory pathway" in a study where efferent vagal output was shown to effectively inhibit pro-inflammatory cytokine release and result in a systemic anti-inflammatory effect [36]. Subsequent work identified signaling by nicotinic acetylcholine receptors as an essential component of the cholinergic anti-inflammatory pathway which eventually causes inhibited activation of NF-κB and reduced production of TNF [37,38]. What brings the cholinergic anti-inflammatory pathway to the forefront of clinical research for chronic pain management is the fact that these cholinergic effects are by no means limited to areas innervated by the vagus but are evident in distant parts of the gastrointestinal system as well as in the cardiovascular and musculoskeletal systems being able to affect blood pressure levels and modify the course of rheumatoid arthritis [38-40]. Currently, this systemic effect is primarily attributed to the expression of choline acetyl transferase on CD4+ lymphocytes [39]. The theoretical basis of the cholinergic anti-inflammatory pathway has been presented along with a view of the clinical implications of the bidirectional signaling and mutual activation which can take place in the interface between the nerve and the immune system in order to affect the onset and maintenance of chronic inflammation [41]. This line of research appears promising as there is already the precedent of vagal nerve stimulation in the treatment of epilepsy which has proved quite successful [42]. Vagal stimulation for the management of epilepsy results in increased norepinephrine production in the locus coeruleus but its associated immune responses have not been studied. Also, since the function of the vagus is almost entirely motor, with a minimal sensory component, the occurrence and nature of retrograde (afferent) activation may be relevant.

The immediate clinical implications of the existence and function of a cholinergic anti-inflammatory pathway are quite significant since allergic CV is typically associated with marked pruritus and antihistamines are routinely prescribed for control of symptoms [10]. Antihistamines are, in general, anticholinergic medications. Their anticholinergic effects were more prominent in the first-generation antihistamines but second-generation products, including those with an excellent profile vis-à-vis crossing of the blood-brain barrier, are not free of significant anticholinergic activity [43]. In the course of CV, treatment with potent antihistamines is often necessary; one has to wonder whether long-term uninterrupted treatment with antihistamines does not actually deprive the patient from useful anti-inflammatory cholinergic effects. In the opinion of the authors, brief courses of antihistamine treatment for suppression of pruritus have been rewarding. However, if relief has not been achieved within a few weeks of antihistamine treatment, prolonged use is not likely to provide relief. On occasion, use of β-agonists has been successful in controlling pruritus but, in general, the efficacy of oral terbutaline in the management of pruritus is doubted [44]. Considering the fact that β-agonists are mast cell stabilizers, the failure of terbutaline to control itching may be related to terbutaline-related suppression of the cholinergic anti-inflammatory pathway described by Pavlov and Tracey [36,41]. In fact, there is one animal study where increased skin expression of TNF-α, heightened production of IL-1β and enhanced responses to serotonin were reported as a direct result of long-term treatment with terbutaline [45]. Other mast cell stabilizers, such as cromolyn, have fallen in disuse when it comes to chronic pruritus. These observations raise the question of priorities in the management of chronic pruritus in allergic CV, and suggest that mast cell stabilization and antihistamine action may be of lesser importance when weighed against the possibility of loss or suppression of the anti-inflammatory cholinergic anti-inflammatory pathway.

Patients with CV will often complain of loss of efficacy of antihistamine treatment over time. Tachyphylaxis is not known to

occur in H1 receptor blockade. In fact, a study which addressed this issue in allergic rhinitis patients treated for 180 days with cetirizine or levocetirizine found no evidence of tachyphylaxis [46]. Furthermore, once response to initially prescribed dosing is lost, subsequent response to increasing doses (the hallmark of early tachyphylaxis) is not observed in patients with allergic CV. It is hypothesized that the perceived loss of efficacy over time may represent the effects of antihistamine treatment on the cholinergic anti-inflammatory pathway. There are, however, two antihistamines to be considered in the long-term management of allergic CV:

Hydroxyzine, a potent first-generation antihistamine, in addition to H1 receptor blockade, has significant anti-serotoninergic and anxiolytic activity. The safety and efficacy of hydroxyzine is such that hydroxyzine is routinely recommended in the management of generalized anxiety disorder, alone or in combination with an SSRI/SNRI or with buspirone [47]. Long-term treatment with hydroxyzine in allergic CV has been effective for large numbers of patients who fit an anxiety profile.

Cyproheptadine is another first-generation antihistamine with remarkable anti-serotoninergic activity. In fact, its anti-serotoninergic effects are such that cyproheptadine is used as a first-line drug in the management of the serotonin syndrome [48]. Cyproheptadine is a useful addition to SSRIs/SNRIs when sexual dysfunction develops in the course of treatment with SSRIs/SNRIs because it can reverse this side effect and also allows for improved control of symptoms without further increases in SSRI/SNRI doses [49]. Cyproheptadine has a powerful inhibitory effect and an excellent safety and compliance record. It is also one of the first-line drugs in the management of migraines and cyclical vomiting in childhood. In a series of 4,839 patients aged 2-17 years, evaluated over a period of four years, cyproheptadine was one of the five most frequently used drugs in the management of migraines [50].

Anticonvulsants

Barbiturates, carbamazepine and valproate have been used in the management of CV with excellent results as far as efficacy is concerned, but with varying degrees of tolerance, compliance and safety while liver enzyme induction, enzyme inhibition and interactions with other drugs remain a major concern. The use of anticonvulsants in the management of CV has recently focused on topiramate, an anticonvulsant originally used with success in the Lennox-Gastaut syndrome, tried in post-traumatic stress disorder and cluster headaches, frequently prescribed for migraines, and regularly used in the management of neuropathic pain [51]. Its efficacy and safety profile are such that topiramate is now one of the choices that tend to replace the first-line drugs traditionally employed in the three-tier approach to chronic pain recommended by the World Health Organization. This three-tier approach previously recommended the gradual use of non-steroidal anti-inflammatories, followed by soft opioids (tramadol, codeine), followed by hard opioids (morphine, oxycodone, fentanyl). Emerging data called for a change of this model and currently the Spanish Pain Society and the Canada Pain Society have issued guidelines which support the use of topiramate as one of the three first-line choices in the treatment of neuropathic pain, the other two being GABAergics and various antidepressants alone or as combinations [52]. In addition to neurotransmitter level changes in the brain, suppression of pro-inflammatory cytokines following treatment with topiramate has been demonstrated-a familiar pattern with most of the neuromodulators used in the management of CV. Topiramate suppresses the expression of IL-6 in the hippocampus of epileptic rats [53]. In patients with migraines, topiramate caused lowered IL-6 levels [54]. Adverse effects are rather common, that is, their incidence exceeds 10%. Fatigue, somnolence, dizziness, weight loss, memory impairment, intention tremor are reported as well as a large variety of other, less common ones. In general, however, when compared to other anticonvulsants, topiramate is very well tolerated.

Immune suppression/modification

Suppression of inflammatory activity is a target of allergic CV management. The neuromodulatory effects of immune suppression are quite diverse and their discussion is beyond the scope of this study. Nonsteroidal anti-inflammatories and leukotriene blockers have been used in the management of CV with moderate success. Anti-rheumatic disease modifying agents, such as hydroxychloroquine, have been tried in small studies, usually in combination with topical steroids, with notable success in select patients whose profile was suggestive of autoimmunity [55,56]. There are no studies assessing the use of dapsone. Experience in the management of allergic CV with non-steroid immune suppressants, such as cyclosporine, methotrexate and azathioprine, is quite limited but appears promising; yet no published data are available. Regarding mycophenolate mofetil and cyclophosphamide, even anecdotal information is lacking.

Conclusion

Beyond the management of specific co-existing abnormalities, such as infections, allergies, operable conditions and hormonal aberrations, which often accompany the pathology of CV, chronic pain, pruritus and anxiety need to be treated as they are manifestations of pro-inflammatory processes which have a significant impact on the course of CV. There are a large number of available therapeutic modalities. Treatment choices should be individualized and largely determined by specific types of clinical presentation. Long-term neuromodulation in allergic CV may follow one of six approaches:

- GABAergic modification,
- Antidepressants,
- Cholinergic amplification,
- Select first-generation antihistamines with established anti-serotoninergic activity,
- Anticonvulsants, and
- Immune suppressants.

These general modalities are not mutually exclusive and their combinations are often necessary for optimal outcome. The original choice of a neuromodulator may require augmentation to better control symptoms. Guidelines for such additions are available. These therapeutic options are not employed in equal measure as the current level of understanding and implementation for each one of them varies widely. At this point in time, GABAergic modification is the one area where the most experience has been gained, with expansion of knowledge in other areas of neuromodulation expected.

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