POSTHERPETIC NEURALGIA IN THE ELDERLY: AN UPDATE

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Summary

The leading scientific, neuroscientific and pharmacological literature was searched to gain insights into the role of central learning, memory formation, and synaptic field plasticity circuits down to neuronal subunit domains, and into their possible involvement during and after the recurrence of postherpetic neuralgia due to varicella zoster virus in the elderly, as a basis of innovative therapeutic and preventive treatment.

Key words: Elderly. Postherpetic neuralgia. Basis of drug treatment and prevention.

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Erroneousness leads to a closeness from which one can take what is exact. False statements are often an ambiguous terrain and the best route to arrive at what is right. Herta Müller, Gelber Mais und keine Zeit, Care Hansen Verlag München.

In: Le vie Sottili, La Biblioteca di Repubblica-L' Espresso, 2011, p 73.

Prélude inoffensif; Spécimen de l'Ancien Regime
Péché de veillesse

According to Rachel Jordan's Editorial in the *British Medical Journal*, it is not the elderly who should be vaccinated, given their weak and poorly reactive immune system, but those who work in direct contact with them. In the opinion of Sergio Mariotti (in *Epicentro*, the epidemiology journal of Italy's Istituto Superiore di Sanità) and Tom Jefferson (again in the *British Medical Journal*) there is no evidence of the usefulness of flu immunization campaigns, especially where the elderly are concerned [1]. Proteotoxic neurodegenerative processes associated with stress may be weakly contrasted in older subjects [2], and the activation of (spinal cord) microglia via $P2X_4$ and p38-MAPKinase purinoceptors, which intervene in neuropathic pain [3], may exhaust the immune system of the human brain [4], which is characterized by the complexity of glial astrocytes [5]. The genetic cascade controls the specification of behavioural blueprint neuronal circuits [6]. A greater knowledge of dopaminergic differentiation could open new therapeutic prospects [7], and in relation to the scope of this paper, the mother's oxytocin itself affects the inhibitory switch of GABAergic mediation, which participates in the rewiring of different anatomical, physiological, and synaptic functional levels, and in those involved in the intrinsic neuronal circuits of epileptic syndromes [9]. The intrinsic neuronal synaptic plasticity and learning ability characteristic of the hippocampus and neocortex [10] have become quite well known in relation to the same characteristics of the brain in general, something that also applies to the elderly [11]. The state of the art in the cited fields shall be recalled in the present Update both as regards innovative data found in the spinal cord and higher-level pathophysiological integration. At the time of the introduction of a new vaccine, *Zostavax*, in 2005, to prevent herpes zoster virus (HZV) and postherpetic neuralgia (PHN) in those aged 60 years or older [12-15], the issue of therapeutic vaccination had already been addressed since 2003 independently of the broader analysis of the most recent aspects of the diagnosis and follow-up of the disease [16]. The question being asked then was whether the vaccine would be beneficial in maintaining and repairing the lesioned spinal cord, helping its self-healing process [17]. At that time the goals of Spinal Cord Injury Response (SCIR) had already been specified [18].

1. General scope.

1.1. Among the greatest challenges and opportunities of science, technology and social policy, discussed by the President of the American Scientific Association, group 3- Global health, are the treatment of infectious diseases and of latent and chronic infections by new immunological methods [19], while the study of memory persistence has been very successful [20]. The reader

is referred to the 453 bibliographic references of a recent paper re-examining the placebo effect for a clearer and necessary reclassification (molecular as well as therapeutic) of receptor specificity and selectivity [21], which is of practical relevance for the present study, as will be apparent below. The results achieved in the interval have, moreover, extended and added to the conclusions drawn then. When making decisions, a greater sensitivity to loss depends on the expectations of advantages and on previous experience in the same regions activated by similar benefits, with interindividual differences in risk assessment that result in opposite behaviours – specifically in the insula for addiction to smoking [22]; ambiguous decisions consequent to the sensory input are preceded by a predictive perception in the medial frontal cortex, in a remote connection exchange with sensory perception [23]. Most of the brain's energy expenditure is however apparently related to aimless electrical-metabolic "wandering", independent of any stimulation [24-27], which clearly increases the contribution of unconscious compared with conscious processes [Cf. 28]. The intraindividual variability of behaviours, also in the elderly and in traumatic processes, correlates with central, predominantly frontal, neuronal structures, neurotransmission and activity [29]. However, memory mechanisms (not only those for the distant past) as well as imagination, a so-called memory of the future, are located in the hippocampus, also in the elderly [30-33], in a way that is reminiscent of the olfactory system [34]; here studies have been conducted into the simultaneous existence of excitation offset by inhibition of spinal cord centres [35-36], modulation of the information-processing that contribute to schizophrenic deficits [37], that extend to the development of neurodegenerative processes as in Parkinson disease, besides the identification of the (rare) genetic-familial forms, and to those involving the pathogenic evolution of different modulation and control pathways [38] (e.g. the dopaminergic pathway but also the predominantly A_{2A} purinergic pathway, which has finally made it to clinical practice [39]). In effect, the traditional neuronal pathways are increasingly associated to others, designated "corollary" [40], generated by the evolution of variously interactive internal processes. Different molecular cascades are involved in the different brain areas where memories are consolidated [41].

1.2. New technologies have achieved successes that cannot be reached with PET and even less with functional magnetic resonance imaging—or promise to achieve them shortly—at the lower, even "reductionist" molecular levels [42-47], allowing definition of supramolecular redox potentials [48-49] as mitochondrial longevity [50-53]. As regards the present discussion, a hippocampal gene has been identified (*Kibra* alleles), whose activation ensures memory retrieval [54]. An important related issue being addressed is the meaning of the expression of nucleotide

variant copies in the expression of genetic phenotypes [55] and of haplotypes–in the three human variants of the gene of catecol-O-methyltransferase, regulator of cognitive functions, affective moods and pain perception [56] –compared to single polymorphisms, even those considered silent, which nonetheless alter substrate selectivity [57-58]. Synaptic autophosphorylation of αCaMAP-kinase II, tyrosine-kinase Fyn and NMDA and AMPA glutamatergic receptors, modulated by tyrosine phosphatase (STEP) [59-67], has a role in synaptic plasticity processes, while the kinetics of learning have definitively been identified, as have early hippocampal memorization of initial early LTP, calcium-dependent and independent of protein synthesis vs those of the maintenance of nuclear late LTP, of mRNA transcription of atypical isoprotein kinase–C zeta, constitutive, that requires neither calcium nor diacylglycerol for activation, inhibited by phosphorylation of GluR1-AMPA subunits, induced, different, selectively associated with depression, retrograde amnesia and erasing of even long-standing memories, LT inhibition [68-70]: administration of ZIP inhibitor, permeable peptide acting on the domain of PK-zeta self-regulating selective phosphorylation, capable of effective inhibition of classic synaptic LTP by high-frequency impulse trains (ZAP), has contributed to results considered among the most brilliant in 2006 [20]. Activation of cascades of gene expression is a universal feature of long-term memory processes, and stored memories can become temporary vulnerable and cancelled, as reconsolidated, reorganized and enhanced (i.e, in the rat, by insulin-like growth factor II, IGF-II, also known as IGF2; Cf [71]), nevertheless these studies have not been performed in any PHN model yet.

1.3. In this phase of accelerated evolution of the experimental references required for the clarification of the rationale of innovative ethical treatments, physicochemical, modelling and related mathematical and statistical analyses as well as clinical trials and broader social pharmacotoxicological studies [Cf. 72] remain critical. In addition to the numerous citations listed in the Supplement [73], here we recall the most salient contributions, as usual in inverted temporal order in the two groups [74] and [75].

2. Notes on the pathophysiology of pain syndromes, from the spinal cord and beyond.

2.1. This is clearly not the place for an extensive examination of current integrated, homeostatic, cognitive interpretations of pain. According to the International Association for the Study of Pain (IASP), pain is “an unpleasant sensory and emotional experience associated with actual or potential tissue damage” related to syndromes classified as *nociceptive*—physiological because protective, i.e. useful for lesion repair—or *neuropathic*, i.e. related to lesion or dysfunction of the

CNS (e.g. stroke and those associated with Parkinson disease) or PNS [e.g. PHN, peripheral diabetic neuralgia (PDN), trigeminal neuralgia, nerve entrapment neuralgia], which are maladaptive, tend to be chronic and have no protective role. The reader is thus referred to [76].

2.2. The evolution and sequelae of PHN, which are not sufficiently investigated even though they are substantially different from PDN and traumatic (including postoperative) neuralgias, can involve multiple sensory districts including the oculomotor, trigeminal and facial areas, with risks that can be increased by locoregional ophthalmic and auricular complications. Nonetheless, considerable research, also using standardized animal models, has been devoted to spinal cord neuralgias, principally those related to pain syndromes due to sensitization, hyperalgesia, associated with excessive and/or allodynic evoked responses (caused by normally non-algogenic stimuli), even though visceral sequelae, vegetative (including motor) dysfunctions and comorbidities, such as sleep disturbances and anxious-depressive conditions, can arise in other districts and in correspondence with injured dermatomeres. All such conditions considerably impair quality of life and generate disability that can be socially quite severe. Sometimes sensory and motor pathophysiological dynamics, identified at the level of the spinal cord, have preceded and represented major reference models for the in depth functional studies reported for higher and more complex integration levels as well as for current cellular and submolecular ones. A new analysis [77], published after the original observations made in the 1950s and 1960s, has addressed the implications of spinal lesions that deinhibit somatic and visceral motor activities that can be referred to a persistent postnatal functional triggering tone by predominantly thermal modalities, which can be acquired by the adult animal using selective conditioning as well as pharmacological media [78]. The most recent model of balanced inhibitory and excitatory discharge frequencies in spinal motor neurons, varying in phase, not out of phase [35-36], evolution of spatial time and frequency domain models [Cf. 77], could maybe be extended here to those cited above involving spinal facilitation of NMDA receptor currents, via intrasynaptically released glycine [61], a molecular contribution already hypothesized to trigger inflammatory hyperalgesia, potentially already codified as a predictive reward of the amygdala extended to the human orbitofrontal, anterior cyngulate cortex, and so on up to the pharmacological modulation of perception learning and associated cortical reorganization [Cf. 79]. A further route, dating back to the myth of Er, described in Plato's The Republic and revisited by Arthur Schopenhauer and by the present fad of "philosophical concealing", takes us back to the (personal) experience of pain where reconciliation with reality requires a reflection on the different meaning that the world can take for conscience [80].

2.3. The models of spinal pain sensitization processes [81], honed and extended for instance to those of axon regeneration [82], entail the same uncertainties as any translational approach [83] and hence the need for systematic investigation of all available experimental evidence before exposing patients who have given their informed consent to any safety risk, if the treatment is to be effective. This is the case for instance of the experimental research into NK1 receptor antagonists (such as *aprepitant* and *lanepitant*) expressed in dorsal horn layer 1, which have been found to be antihaemetic and antidepressant, but not analgesic, probably due to interference by the well-known control of spinal excitability via the descending pathways, which exert a balanced excitatory and inhibitory feedback [84]. Substance P NK1 receptor has been seen to affect synaptic plasticity in the modulation of hyperalgesia through low-threshold, voltage-dependent T-type Ca^{2+} channels with Ca^{2+}-mediated LTP facilitation [85], more recently confirmed to be different in this setting compared with experiments with high-frequency ZAP [86]; the latter have been found to amplify neuropathic pain also in presence of pre- and postsynaptic low-afferent input inhibitory tone of the first sensory synapse, as shown in inflammation processes, but with collaterals of different selective spinoparabrachial pathways from NK1R-expressing neuronal pathways. It also seems to be undeniable, where lesions evolve as inflammatory processes, that in the context of the resultant "extracellular broth" the effectiveness even of the same antagonists cannot rest merely on isolated effects of their action, but rather on the action towards agents dominating the spectrum of complex local interactions, a fact that unfortunately is not sufficiently tested in current models and in preclinical studies, which have been indicated to be required to precede the ethically inspired marketing of new therapeutic agents. A large number of other different factors analysed in detail but not in the full range of theoretical and experimental conditions, have led to the failure of missed conclusions, for instance for some ephrin ligands involved with their EpH-tyrosine kinase receptors in the embryonic development of circuits crucial for the control of central patterns that in the spinal cord generate locomotion processes [87], also described as regulators of sensory connections modulating the persistence of hyperalgesia [88]. The same is true of the potential implications of neuropathy treatments with selective agonists and antagonists of functional spectra (including opposing ones), analogous to the "twin" peptides tyrosine with 36 amino acids (NPY) [89] and galanin with 29 [90]; of PGE_2EP_1 receptor antagonists [91], also agonists of the receptor associated with alfa-3 glycine [92] as well as of antagonists of the receptor of transient receptor potential cation channel 1 (TRPV1) [93], of B_1 kininic [94] and of leukocyte recruitment in inflammation contexts, purinergic P2Y2 and A3 [95] and finally of neurotrophic factors (BDNF)

acting on trkB receptor at the sites of memory formation and of algogenic, hippocampal as well as spinal dorsal horn mechanisms [96].

2.4. The overall picture that emerges from the more complex mechanisms of holistic integration at the level of the organism and of the individual up to those of the neural tube, has at last reached those of descriptive recall of (polymorphic) polyenzymatic receptor units, dynamically structured in plastic adaptations of philo-ontogenetic development, possibly repeated in the implications of functional pathophysiological regeneration in supra- and intracellular functional networks in modulation and control chains, where the effect of drug administration can no longer be ignored. Specifically, the functional phenotypic units, identified and classified in ion channels, clearly under genetic control and functionally constitutive, or upgradable/inducible potentially in rotation of equilibria between resting (closed) or else variously activated (open) forms, represent sites that dynamically and kinetically condition the pharmacological effects of interest [97], however detailed. Now, among the various groups, subgroups, and polymorphic variants of subunits-channels that over time have been associated with the diagnosis of neuropathy evolution, failed treatment and functional rehabilitation/recovery, despite some major successes, cation proton, acid-sensing ion channels (ASICs), belonging to Na^+ channels, are particularly important. Here at least six isoforms are encoded by 4 genes, the most significant of which, in humans, is ASIC3 [98]. Then there are the thermal ones, transient potential receptor (TRP) channels with different thresholds, of which the above cited TRPV1, previously denominated capsaicinic and/or of vanilloid receptor 1, coactivated by ATP and bradykinin via P2Y2 and B_2 receptors and, as cited in [63], by PIP_2, synonymous with PtdIns(4,5)P_2, phosphatidyl-inositol-4,5-biphosphate – see also [48] and [62] -; the same P2X group, seven subtypes activated by extracellular ATP, mainly P2X3; and also the voltage-dependent Na^+ channels, encompassing 9 α subunits and one or more accessory ß units, subdivided into tetrodotoxin-sensitive and -insensitive [99]; as well as the traditionally more explored ionotropic ones, subgroups of glutamate and nicotinic, and finally the best known and significant, Ca^{2+} channels, L, N, P/Q, R and T subtypes, made up of α_1 subunits, constituting the pore, and of accessory subunits α_2, ß, γ and δ, assembled with BK_{Ca}, and K^+ channels, also voltage-dependent [100]. Even more recently, especially through selective gene knockout, it has been demonstrated by mouse electropharmacological experiments that of the four-member family of HCN ion channels, the $Na_v1.8$-HCN2 isoform, cyclic AMP-dependent, is specifically involved, via a mediator that influences prolonged voltage-dependent activation of small primary nociceptive

sensory neurons with an apparently normal threshold, in the inflammatory and/or thermal hyperalgesia of neuropathic pain [101].

3. Pharmacological aspects of treatments.

3.1. As stated throughout this paper, the current pharmacopoeia must take into account the most complete evidence possible from the "–omic" fields. In fact, there where the constitutive molecular structures and associated dynamics and kinetics can be identified at the genomic, proteomic and metabolimic levels, it is possible to descend to the level of the individual pharmacopoeia and to define the number of pharmacological targets [Cf: 102]. At the same time it will be possible to build "from the base", using some modelling tool, which has been defined and cited above (Cf: estimate of interactions and their clusters [74]), a thesaurus of iterative frequency analysis data with a view to establishing the highest likelihood of the most useful and least risky adaptations for the diagnosable subgroups of treatable conditions, as an evaluation of convergencies between significant aspects of essential or inessential drug products and those of the interacting domains of the major targets for the recovery of normal ranges. Well, according to current evidence, the treatment of neuropathic pain, whose pathogenetic and pharmaceutical dynamics is better known than that of other syndromes, is impossible to standardize due to very frequent "off-label" prescriptions, something that has been viewed as the consequence of poor preclinical and clinical experimentation, resulting in turn in highly unstable classifications (Cf: [21]). In particular, PHN has been indicated as the most widely used condition in the investigation of new principles, in research less empirical and more soundly rooted in biomedical rationales specifically validated for hypersensitivity models, rather than in dominant hyposensory pictures, for instance of diabetic neuropathic pain, which are similarly chronicizable [103]. These authors however cite for postherpetic syndrome a very discouraging situation in terms of effectiveness compared with the known risks of the most widely used drugs [104].

3.2. In substance, after administration of antiviral treatment after the diagnosis–possibly associated with cortisone therapy, which however does not always prevent the onset of neuropathy (see Whitley, 2009 [105-106])—the patient is generally given *topical anaesthetics*, (e.g. a 5% lidocaine hydrochloride ointment) ligands of non-specific Na^+ channels, sometimes with occlusive bandaging, as protection from and prevention of abnormal central inputs from ganglion neurons, considered as participants and causes of the rewiring resulting from potential disease chronicization. The patient is also prescribed non-selective tricyclic *antidepressants* (amitriptyline, i.e. *Laroxyl*, or others) - 25 mg/24 h -, or else imipramine, nortriptyline,

desipramine and others; more recently venlafaxine, duloxetine (*Cymbalta*), milnacipram, and sometimes bicifadine, which selectively blocks central noradrenalin and serotonin reuptake, possibly in addition to drugs aiming at glutamatergic and glycinergic comodulation, although these have not clearly been found to be effective. All such agents have been widely investigated in chronic pain conditions, but in neuropathies of different origins, and suffer from a lack of specificity at the anatomical sites involved and, even more, from a lack of subreceptor bond selectivity. Besides—and this does not apply solely to amitriptyline, administered to the elderly to allay stress and help restore CNS injuries by enhancing nerve recovery—some believe that stimulating neurogenesis, which is not always effective, may be counterproductive [107]. Other voltage-dependent Na^+ channels resistant or sensitive to tetrodotoxin have been used, like antidepressants and analgesics (e.g. carbamazepine), antiepileptics like fenitoyn, topiramate, lamotrigine, ralfinamide and levetiracepam, which are effective against other neuropathies, or the cited TRPV1 blockers, like topical capsaicin, desensitizing due to peptide depletion, which has been shown to be effective in PHN, and analogues free of adverse side reactions like bronchoconstriction. In addition, *anticonvulsives* for partial attacks, localized or otherwise, have also been prescribed in adults, especially GABAergic enhancers, also developed to treat adult *generalized anxiety*, another agent introduced empirically and nonetheless found to be effective in several large controlled clinical trials: first of all gabapentin (*Neurontin*) and more recently pregabalin (*Lyrica*), registered as a lipophilic cyclic GABA analogue in the stable form of the S-[+] enantiomer of 3-isobutyl-GABA when the patent of the former expired on July 30 2005. Here we cite only the clinical studies of PHN [108], but the newer "me too drug" has replaced the original agent (and not only in this chronic algogenic neuropathy), with demonstrated effectiveness at daily doses of 150 to 600 mg, whereas doses of 1600 mg/day gabapentin were easily reached. Reports by AIFA, Italy's drug regulator, have shown that the frequency of suspicious reactions reported in Italy is similar to that described elsewhere [109], whereas other studies have noted a lack of comparable investigations, since the patients recruited for the pregabalin study were refractory to the precursor [110]. In the experimental investigations, the two "me too" drugs included were nonetheless found to have overlapping pharmacometric profiles, with a presynaptic selective action site via the accessory $\alpha_2\delta$ subunits of voltage-dependent Ca^{2+} channel receptors, where pregabalin displaced the previously bound gabapentin, and both reduce release of a number of excitatory agents, including noradrenalin and glutamate, and maintain cellular levels of GABA and glutamine [111]. Clinically pregabalin is most effective against pain 1 h from oral adminsitration at fixed times, BID or TID; its metabolization rate is only about 2%, renal excretion correlating with creatinine clearance. It is associated with a

number of adverse reactions, all reported in the drug information sheet; the most severe, though uncommon, are vertigo, ataxia, sleepiness, weight gain, peripheral oedema, and urinary incontinence. The dose must be doubled each week and discontinuation must similarly be tapered to avoid recurrences, rebounds and withdrawal symptoms that are being investigated.

After demonstration of the activity (or lack thereof, as in the case of the cited NK1 receptor antagonists) of non-peptidic neuropeptide antagonists like devazepide and the prototype proglumide against colecystokinin (CCK)-1 and especially -2 receptors, albeit again only for chronic pain related to other neuropathies, modulators of the opioid system, of bradykinins especially B_1, and of release not only of peptide P, buy also of calcitonin gene-related peptides (CGRPs), like cizolirtine, are being developed. Finally, the traditional treatment of chronic pain with opiates [104] has been made easier in Italy by Law no. 12 of 8.2.01 and by the AIFA provisions of 31.12.04, and is actively being investigated [106] also in relation to the typical adverse effects, like respiratory depression with 5-$HT_{4(a)}$ agonists [112]. After demonstration of its synergy with central α_2-agonists like topical clonidine (*Catapresan TTS*, transdermal patch), it has been recommended as a first-line treatment for PHN, also in rotation, especially with levorphanol – which binds to μ_1, k and δ receptors – and racemic methadone, both of whose isomers bind the NMDA receptor [113], and is considered more effective than antidepressants in the treatment pf PHN [114]. The formulation combining morphine and gabapentin has been found to be especially effective [115], since association studies with pregabalin are as yet unavailable (°). Relevant to the topic, immunodepression due to UV radiation is related to absorption of the radiation energy by cutaneous *trans*-urocanic acid, which isomerizes to *cis*-UA with obligatory bond to 5HT receptor; the bond is required to mediate the immune response which in turn is prevented by 5HT antagonists like ketanserine [116]. The itching nearly always associated with neuropathic pain is mediated by lateral spinothalamic tract histaminergic neurons, found in layer 1 of the posterior spinal horns, here involved with those more notoriously algogenic, overwhelmed by the PHN "inflammatory soup" [117].

3.3. After mentioning the prospects of macromolecular biologics being developed for human anti-neurotrophic factor (NGF) antibodies [103], with reference to NGF and trK receptor

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(°) "Pregabalin associated with opiate in postherpetic neuralgia (PHN)": no clinical trials found in November 4, 2011 with an advanced Google search. In the same 790 contacts and around 66,300 hits pregabalin was found to decrease opioid requirements; additive CNS experience is possible, but very effective during the withdrawal syndrome; etc.

pharmacodynamics in pain syndromes [96], including epileptic syndromes [118], we go back to the Introduction, where we mentioned the recent approval by the FDA and the EMA of the attenuated HZV vaccine, made from the Japanese Oka strain (*Zostavax*), containing about 19,400 plaque forming units (PFU), to prevent chickenpox in children and shingles and neuropathic complications in healthy adults aged 60 years or older [12-15]. The vaccines introduced in the USA in 1995, sold in Italy from 2002, contain ca. 1,350 PFU (*Varivax*, monovalent) or 9,772 PFU per dose (*ProQuad*, quadrivalent) [119]. The randomized, double-blind, placebo-controlled reference study, with a mean follow up of about 3 years, conducted on 38,546 immunologically competent individuals with a history of chickenpox aged 60 years or older [12], documented a 61% reduction in the severity and duration of pain and diseases burden; a 64% reduction in herpes zoster incidence in the 60 - 69 year age group and a 38% reduction in 70-year olds; and finally also a 67% reduction in PHN in subjects older than 70 years. The results suggest that after the first infection (which in adults is more severe) the virus remains latent in sensory ganglion neurons of the whole neural tube (cranial nerves III,V,VII, dorsal spinal and autonomic), stimulating cell-mediated immunity (CMI); CMI progressively wanes in the elderly, and can be restored by more powerful vaccine doses. CMI declines below critical thresholds typically happen with frequencies < 5%; this rate climbs to 50% after age 60 years and even higher afterwards, causing neuronal death and demyelination as well as inflammation associated with neuropathy. PHN usually does not arise before 50 years of age; its incidence is about 40% in 60 year olds and 50% in 70 year olds, and the pain persists as long as a year after rash resolution. PHN may be compounded by comorbidities such as radiculitis, myelitis, granulomatous vasculopathy of large vessels–including cerebral arteries, 7 weeks to 6 months from the rash – and/or of small vessels, associated with enkephalitis, ventriculitis and meningitis [120], which entail further deterioration of quality of life. All such complications may also arise without a rash, as shown by PCR analysis of viral DNA and by antibody titers. Immediate subcutaneous administration of a single *Zostavax* dose (0.65 ml) after reconstruction has been recommended since October 2006 for subjects > 60 years of age, including those with a previous HZV episode. It is contraindicated in pregnancy, untreated tuberculosis, immunodeficiency, lymphoproliferative malignancies and cytotoxic (including cortisone) treatments. The drug has not been associated with severe adverse reactions. The study of protection duration and of dose and boost requirements, especially in the elderly, is under way (Cf [121]). However cost analysis of direct treatment has found an overall gain compared with the savings obtained from the need not to treat complications [14].

Clearly, it would also be interesting to investigate whether synthetic active tryptophan autocatabolites, including orally administered ones [122], may contribute to the treatment of neuron inflammation. Another suggested trial?: The extended proteomic research in model rats ([123]; see Google on mice, etc) with the JZL184 prototype monoacylglycerol lipase (MAGL) inhibitor, to be translated on human PHN, to obtain anatomical segregated specific and selectively targeted preventive reduced chronic antiinflammatory prostaglandin inflammation, associated with properly modulated endocannabinoid signalling, heightening the brain's own protecting mechanism, sparing the cardiovascular adverse reactions, as the haemorrhaging caused by COX inhibitors in the gut.

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