OPEN ACCESS Freely available online

Journal of Aging Science

Review Article

Inflammation, Delirium, Dementia and Ageing Brain Phenotypes: A Short Review and the Need for New Approaches to Explore Immune System Complexity

Stephen C Allen[1,2*]

[1]*Department of Medicine, The Royal Bournemouth Hospital, Dorset, UK;*[2]*Centre for Postgraduate Medical Research and Education, Bournemouth University, Dorset, UK*

ABSTRACT

Ageing is associated with persisting systemic inflammation, both in chronic form and as delayed resolution after acute inflammatory illnesses. The clearest markers of this are raised blood concentrations of pro-inflammatory cytokines and other chemokines that are involved in mediating an inflammatory state, and C-reactive protein as general indicator of inflammation. This condition of "inflammaging" is linked causally in a complex and reciprocal manner with several diseases that are prevalent in older people including a tendency to develop delirium during acute perturbations of brain function, and to a predisposition to dementia and other age-associated neurodegenerative conditions. There is evidence of a key role of cytokines both in the aetiologies of such diseases and in the immune modulation processes that reduce inflammation, and evidence that interleukin-6 has a particularly complex effect depending on physiological and metabolic context. It is probable that the influence of cytokines on the central nervous system is directly mediated via receptors on neurons, microglial cells and astrocytes, rather than through secondary metabolic effects. The epigenetic mechanisms involved are starting to be understood. Though the descriptive phenomenology of inflammation has produced a large amount of information it is obviously, like the biochemistry of all living organisms, an extremely complex environment that cannot be described adequately using linear pathways, or even 3-dimensional models. To deal with the complexity, fluidity, stability, responses and fluctuations of immune chemistry it is proposed that a better grasp of immune system regulation, its responses to perturbation and its relationship with disease states and aging, including neuropathology, might be better progressed by using a multifactorial conditional logic approach, such as Boolean analysis. Such work will require an iterative collaboration between clinicians, molecular biologists, mathematicians and software engineers.

Keywords: Inflammation; Aging; Cytokines; Delirium; Dementia; Brain; Conditional logic; Boolean

LITERATURE REVIEW

Clinicians and bio-gerontologists broadly agree that there is an imperative to define better the mechanisms by which of inflammation, particularly when it is chronic or slow to resolve, has an adverse effect on the wellbeing of older people across several key physiological domains, including Central Nervous System (CNS) function, and that current hypotheses based on molecular aging theories are inadequate [1]. Chronic inflammation and persisting post-acute systemic inflammation have been consistently observed to be a contributary factor underlying the patho-physiological mechanisms that culminate in chronic phenotypic clinical states such as the frailty syndrome, autonomic deconditioning, muscle weakness and overt sarcopenia, impaired cognition, low mood, poor functional performance and higher all-cause mortality [2]. Further, and as a particular exemplar for this paper, there is a rapidly accumulating body of evidence that points to the involvement of immune system biochemical molecular components in the

Correspondence to: Dr. Stephen Allen, Department of Medicine, The Royal Bournemouth Hospital, Castle Lane East, Bournemouth, BH7 7DW, UK, Tel/Fax: +44 (0)300 019 6175; E-mail: drscallen@aol.com

Received: November 18, 2020; **Accepted**: December 01, 2020; **Published**: December 08, 2020

Citation: Allen SC (2020) Inflammation, Delirium, Dementia and Ageing Brain Phenotypes: A Short Review and the Need for New Approaches to Explore Immune System Complexity. J Aging Sci. S3.003

causation of delirium, in both acute and chronic formats, as well as a complex role in dementia [3]. Though the acute effects can apply to people of all ages, the impact on elderly patients tends to be more frequent, more sustained and more chronically damaging [4]. However, despite the substantial amount of extant published research in this area of neuro-pathology the cellular and molecular mechanisms involved are not well understood, and some of the findings appear to be inconsistent or contradictory. Therefore, for the purposes of this paper, a concise review of the current key empirical evidence will be made, including the apparent contribution of pro-inflammatory states to the formation of a number of clinical phenotypes, focusing on delirium for more detailed scrutiny. This will be followed by a consideration of the limitations imposed on developing a sophisticated view of the mechanisms in play due to the pathway-orientated approach that is traditionally deployed in biochemical research. The paper will conclude with a suggestion for a hypothetical alternative model for exploring and understanding the highly complex interplay between immune cells, immune biochemicals and neurons that leads to the brain dysfunction that manifests phenotypically as delirium and other age-associated CNS disorders.

Inflammation and ageing

Chronic inflammation and inflammaging: The initial biochemical responses to antigenic threats, often but not exclusively infections, are collectively referred to as the innate immune response. This form of defence has a robust evolutionary heritage, a relatively stable genome, and is found in recognizable configuration in animals across a wide range of genera [5]. Like all complex systems it can be perturbed, indeed immune function depends on perturbation in the form of an antigenic stimulus to initiate normal function [6], but these characteristics pave the way to potential dysfunction under certain circumstances, such as nutritional deficiency, genetic mutation and some viral pathogens, and there also appears to be a complex effect in individual organisms due to ageing [7]. To form a backdrop to the arguments presented later in the paper it is necessary to look at certain features of innate immune function in older humans, with some reference to other species. It has been repeatedly confirmed that in the intervals between acute inflammatory episodes the baseline titres of chemical inflammatory markers, such as interleukin-1 beta (IL-1β), tumour necrosis factor alpha (TNFα) (referred to simply as IL-1 and TNF hereafter) and C-reactive protein (CRP) are often about 2 to 4 times higher in the peripheral blood of elderly people, particularly people over 80 years of age, when compared with the titres found in healthy young and middle-aged volunteers [8-10]. For example, a study of adults with no clinically apparent illnesses showed a mean baseline peripheral plasma TNF level of 0.6 pg/mL in those age 18-29 years and 1.5 pg/mL in those age above 68 years [9]. Similar age-related differences were found in a community study of CRP, with only minor variation between people of European and African heritage [11]. In this context CRP can be utilized as a broad-spectrum marker of age-associated pro-inflammatory activity and the mean rise with age is taken as indicating a background state of low-level inflammation in elderly people and is sometimes summarized by the term "inflammaging" by certain authors in the field of bio-gerontology [10] or the more recent conceptual alternative "senoinflammation" by others [1]. It is clinically evident that the raised baseline markers of inflammation in a large proportion of individuals are the consequence of overt chronic disease states with a known inflammatory component such as Chronic Obstructive Pulmonary Disease (COPD) or Rheumatoid Arthritis (RA) [12]. In addition, persistently raised biochemical indicators of a pro-inflammatory state are associated in older adults with various pathological conditions that seem to tug the innate immune cellular and chemical milieux from its normative baseline toward persistent low-amplitude inflammation. Commonplace and clinically relevant examples of that phenomenon are central and visceral obesity, arterial atherosclerosis and type 2 diabetes (T2DM) [13-15]. Further, and especially pertinent to the condition of delirium, is the raised suite of inflammatory biochemicals, measurable in peripheral blood, that often persists or resolves slowly after an episode of acute inflammation, typically infection or physical injury [1,16,17]. People suffering from various clinically defined conditions are also known to exhibit persistently raised markers indicative of inflammation. Examples include chronic renal disease, osteoarthritis and physical inactivity, and importantly for the purposes of this paper, such markers have found with a high prevalence in Alzheimer's Disease (AD), [13,18-20] and other degenerative neurological diseases associated with inflammation [3,21,22]. Moreover, elderly people with self-reported good health and no clinical evidence of chronic disease often have biochemical evidence of persistent low-level systemic inflammation, particularly marked by IL-1, TNF, and CRP, with no discernible other cause [10,22-26]. It appears therefore that, depending on an assumption that titres found in younger people define normality, old age can of itself be independently accompanied by a low-amplitude state of chronic inflammation in some, but not all, individuals. For instance, healthy free-range volunteers above the age of 65 were found to have mean plasma CRP titres of 3.0 mcg/mL compared to 0.9 mcg/mL in young adults [23]. Similarly, surveillance-state immune baseline IL-6 and IL-1 titres in peripheral blood also appear to correlate with age [25], though not in all studies [26], possibly due to differing selection criteria for participants [27,28]. So, the arguably simplistic assumption that IL-1, TNF, and particularly IL-6, are always markers of a pro-inflammatory state might not hold true in all circumstances and other interpretations should be considered and taken into account. That issue will be examined more closely in a later paragraph that scrutinizes the function of IL-6. When broadly defined, chronic systemic inflammation appears to be linked with higher overall (all-cause) mortality [29,30], muscle weakness and overt sarcopenia [31,32], reduced functional daily living capability [30] lower self-reported health scores [33], a higher risk of dementia [21,22] and increased susceptibility to delirium [34]. The corresponding plasma markers of inflammation, usually CRP, IL-1, IL-6 and TNF in the cited studies, were found in varying proportions in different studies, depending to some extent on the assay methods and phase-dependent sampling factors, but overall the adverse health effects outlined above were found in those with mean titres around 1.5 to 3 times higher than the levels detected in age-matched well people.

Inflammaging – both cause and effect: With regard to the contribution of inflammation to the pathogenesis of the disease states mentioned above, it is important to take account of the evidence that supports the view that disease predisposition, initiation and progression can be at least partly driven by a chronic inflammatory activity and is not simply an indicator of its presence [35]. The data suggest an intricate relationship between cause and consequence with a mutual augmentation effect. One of the most well-defined examples, inflammation of the arterial endothelium, is of primary importance in the pathogenesis of atherosclerotic disease and can be regarded as a bio-metaphor to gain more general insights into the relationship between inflammation, ageing and pathology [36]. Yet despite its relatively confined range of functions endothelium has very complex functional chemistry and equally complex immune chemistry [37]. Such complexity is repeated in all anatomical structures and is arguably at its most elaborate in the central nervous system. Therefore, by an amplified analogy, the contribution of immune dysfunction to the genesis of delirium, dementia and other aged-associated neurodegenerative conditions, is likely to be extremely difficult to define, understand and model.

Delayed anti-inflammatory resetting: In older age it is necessary to consider other routes through which individuals are more likely to be exposed to prolonged and deleterious systemic inflammation. A proportion of older people, that rises with age, exhibit cellular and biochemical responses to noxious stimuli, mainly infection and trauma, that occur acutely but resolve over a more protracted time course compared to younger adults [16,17]. In those individuals the initial normative elevation of IL-1, IL-6 and TNF in plasma tends to persist longer and the counter-regulatory responding rise in the anti-inflammatory cytokine interleukin-10 (IL-10) is delayed, increases slower and reaches a lower peak titre, compared to young adults. The most consistent experimental evidence for this pattern has been demonstrated with pneumococcal capsular antigen and Gram-negative endotoxin antigen [38,39], for both of which the time taken to return to surveillance immune chemical baseline in older people is about twice that of young adults, despite similar peak inflammatory cytokine titres during the acute phase of the episode. These phenomena indicate that in older subjects there is a change in anti-inflammatory counter-regulation resulting in slower re-setting of the innate immune chemical network to its baseline surveillance mode [40]. Along with the persisting low-level pro-inflammatory milieux outlined in an earlier paragraph, this trend to slow resolution of acute inflammation is a likely candidate for the deleterious burden from immune dysfunction that is commonplace, and possibly ubiquitous, in old age, and it will be posited later in this paper that it pre-conditions the CNS, especially in older age, to various forms of dysfunction and degeneration such as delirium and dementia respectively.

Protective factors: Links between exercise, IL-6, inflammation, CNS function and phenotypic ageing

There is consistent evidence that regular moderate exercise reduces the risk of dementia [41] and delirium [42], and probably improves the rate and quality of cognitive recovery after acute delirium, most clearly the motor aspects [43]. While acknowledging that such benefits of exercise have complex mechanisms and are not confined to immune-system effects there are persuasive data that indicate that IL-6 has a central co-ordinating function. IL-6 is conventionally seen primarily in a pro-inflammatory role, having a wide-spectrum field of influence on innate immune cellular and chemical networks including augmenting the function of IL-1 and TNF, and as a mediator of the insulin resistance consequent upon a sedentary lifestyle. It has long been established that peripheral blood IL-6 titres rise in the initial stages of the innate immune response a pro-inflammatory stimulus [44], typically acute infection or trauma, and are usually also higher, though with lower amplitude, in patients with chronic inflammatory conditions, for example RA [45]. As more empirical data have been gathered, it is now becoming clear that IL-6 has a far more multi-functional role as an intermediate influencer in the control and modulation of innate immune activity that is considerably more complex than that of an early responding inflammatory chemokine [46]. In the context of normal healthy physiological conditions, the main source of IL-6 is actively contracting skeletal myocytes and it has therefore been generally nominated in the myokine group of chemokines [47]. However, IL-6 can be produced in variable quantities, dependent on prevailing patho-physiological factors, by a wide range of somatic cells [44]. Further, when an individual is exercising, the IL-6 released from myocytes has been found to have metabolic effects on the immediate releasing cell, other myocytes, and various other cells such as adipocytes and thereby exhibits functions of autocrine, paracrine and endocrine patterns with profound metabolic effects, of which insulin sensitization is considered to be one of most well delineated [48].

Pleiotropic properties of IL-6: IL-6 is released during exercise across the age range [36,41,49-51]. In research the usual exercise stimulus has been moderate reciprocating exercise, for example cycling or running, though eccentric and isometric muscle action also releases IL-6 [52] and during natural activity all contractility patterns occur in variable combination. In studies of moderate-severe endurance exercise on young adults, IL-6 titres in venous blood can increase more than 100-fold above resting baseline [53] with clear correlations between peak IL-6 titre achieved, and work rate, exercise duration and total work. IL-6 also rises during mild-moderate exercise, such as cycling or brisk walking on the flat for 10–20 minutes [54], this being a work rate that can be achieved by many older people, even those above the age of 80 years [55]. Unfortunately, there are currently no data regarding the IL-6 response to very mild exercise, for example slow walking or domestic ambulation, such as typifies the activity level of frail elderly people, though adopting relatively low rates of physical work from a previously sedentary state have been shown to be associated consistently with a fall in CRP, and, in some studies IL-1 and TNF, which suggests an anti-inflammatory effect [56]. Defining the dynamics of the IL-6 response to exercise is complicated by the finding that baseline concentrations fall to below pre-regimen levels between repeated sessions of exercise separated by several hours [57]. In participants taking part in repeated exercise sessions, whether habitually or during a research regimen, it is not unreasonable to contend that the suppressed baseline IL-6 titres mediate the

anti-inflammatory effect of exercise. Conversely, it seems probable that the short-duration IL-6 rise post-exercise up-regulates insulin receptor sensitivity through a separate effect [58]. Summarily, it can be reasonably suggested that the positive physiological benefits of exercise are mediated by IL-6 via at least 2 broadly definable mechanisms. Firstly, by dampening inflammation through the release of IL-10, IL-4 and other immune modulating cytokines. Secondly, the peak post-exercise IL-6 levels contribute to the maintenance of muscle cell structural integrity and contractility, and insulin receptor sensitization [58-63]. Through recent research these effects are becoming better defined for muscle function and for their involvement in lowering the risk of sarcopenia, but there is a clear parallel with CNS structure and function that requires further empirical work and more sophisticated modelling to improve the understanding of the role of inflammation in the causation of dementia and delirium, its contribution to the progression of the aged CNS phenotype.

Therefore, germane to the arguments in this paper, exercise-released IL-6 apparently initiates the production of anti-inflammatory cytokines, mainly IL-10 [64]. This is probably an important or even essential linking factor between exercise, immune modulation, slowing of the ageing phenotype, including all-cause mortality, and the observed protective effect of exercise on cognitive function, though long-term intervention studies are yet to be completed [65]. Though a complete picture of the influence of IL-6 has yet to be generated it evidently has profound effects on the chemistry of inflammation that is variable, conditional upon immediate and longer-term innate immune needs, and influenced by fluctuations in not only immune chemistry but also other aspects of metabolism and inter-cell signalling; it has pleiotropic properties that are unlike most other cytokines [46-48,64]. To illustrate, during infections and septic states the acute phase release of IL-1 augments the early production of IL-6 and TNF in which case IL-6 appears to behave as a pro-inflammatory cytokine. By way of contrast, as outlined in the paragraph above, after exercise in healthy well subjects the primary secretion of IL-6 facilitates the release of the anti-inflammatory cytokines IL-10 and interleukin-1 receptor antagonist (IL-1ra) [46], thus IL-6 contributes to anti-inflammatory immune modulation. This apparent role flexibility of IL-6, paves the way to understanding the beneficial influence of physical activity on inflammation and the metabolism of carbohydrates and lipids, and sows a hypothetical seed that IL-6 might be even better viewed as both a regulatory cytokine within the innate immune system and as a hormone essential for optimal energy metabolism [66]. IL-6 is therefore increasingly viewed as a cytokine that has a well-documented pleiotropic modulating role in immune system activity, with key functions in the re-setting of innate immune baselines in response to physical activity. Its function as an orchestrating factor on inflammatory activity indicates that it is likely to have a central role in modulating the effect of immune system biochemicals on the central nervous system, including the beneficial effects of exercise [44,46], though there is a paucity of consistent empirical data regarding the molecular mechanisms by which IL-6 operates in that domain.

Inflammation as a driver of neuro-pathology: The changes in immune modulation and baseline inflammation settings outlined above appear to be closely involved in the initiation and progression of a number of clinically important age-related pathologies, including cerebrovascular disease and CNS dysfunction [12]. Of course, it can be contended that all these states can have either direct or indirect effects on the CNS when viewed holistically. The direct impact on neuronal function can be acute, such as is seen in the precipitation of delirium during infection, and is usually reversible. However, chronic and sub-acute inflammation appear to cause insidious changes that are very complex, mainly irreversible and not well understood. For example, there is persuasive evidence that a chronic pro-inflammatory state and the delayed or partial anti-inflammatory counter-regulation that often occurs in older people after acute events contribute to a propensity to develop delirium and can predispose to permanent long-term cognitive decline and dementia [67-70]. Other largely reversible effects include depressed affect, sickness behaviour and autonomic dysfunction [71]. However, an interpretation of the mechanistic contribution of disordered inflammatory responses on the clinical phenotype, time course and severity of these adverse consequences clearly varies in a highly complex and inter-dependent manner depending upon multiple variables, many of which are likely to be as yet unknown, as well as technical issues such as sampling protocols, clinical assessment algorithms and co-morbidities [12,46].

Neuropathological role of cytokines: Though the biochemical responses during inflammation involve multiple classes, such as catecholamines, cortico-steroids, insulin and interferons, the neuro-pathological role of inflammatory cytokines deserves particular mention in this paper because of the increasing evidence of their role in the genesis of delirium and predisposition to dementia [34,72]. Receptors for cytokines that augment inflammation are located on the cell membranes of most neurons [73] and clarifying data are also indicating that certain chemokines and other biochemicals that have key roles in inflammatory responses, such as cortisol and adrenalin, are operational in the regulation and control of nerve cell function, as well as synapse numbers and function, dendritic pruning and neurogenesis [74]. The intracellular and subsequent downstream effects of these cytokines appear to be mediated through receptor-dependent gene switches and those for TNF have been described in detail [75]. Further, receptors for a number of inflammatory chemokines are located not only on brain nerve cells but also on glial cells, oligodendrocytes and astrocytes, including receptors for TNF, IL-1 and interleukin-1 receptor antagonist (IL-1ra), and there are receptors on the same cells for cytokines that are usually considered to be mediators of the modulatory anti-inflammatory type, such as IL-10 [34]. The demonstration of IL-6 receptors on the same cells [34] poses interesting questions about a potential regulatory role within the CNS and it can be hypothesized that at least some of the apparent benefit of exercise on CNS function might be mediated by IL-6 more directly than previously thought. Also, active transport mechanisms at the Blood-Brain Barrier (BBB), mainly located on capillary endothelial cells, and protrusions from neuroglia and astrocytes, have been found to facilitate the

entry of certain blood-born cytokines of systemic origin into the Cerebro-Spinal Fluid (CSF) and brain interstitial spaces, including IL-1, TNF, IL-6 and IL-1ra [74,76]. Moreover, immunologically active glial cells have been shown to respond to cytokine receptor stimulation in a range of ways including augmented release of additional pro-inflammatory cytokines [74]. The consequent rise in CSF inflammatory cytokine concentrations during acute or chronic inflammatory conditions is thus partly due to transport of pre-formed cytokines of systemic provenance from plasma and partly by synthesis and secretion on the CSF side of the BBB. There is an apparent phenotypic translation of these cyto-chemical phenomena. Studies conducted on animals demonstrated that measurable and reproducible changes in certain patterns of behaviour, particularly refusal of food, hiding and increased sleep, closely followed the systemic injection of physiological doses of IL-1 and TNF [71,73,77]. This is clear objective evidence of an acute phase influence of inflammatory cytokines on CNS function. Such observations of brain-level alterations in neural function during inflammation provides a route to guide clarifying research into the cyto-chemical and structural mechanisms through which inflammation can alter high-level nerve function, including a mechanistic framework from which it might be possible to gain further insights into lethargy and delirium. Further, targeted cytokine interventions, coupled with studies of the micro-anatomical changes that occur with age, and in disease states such as AD, are likely to help build an understanding of the molecular mechanisms underlying delirium and dementia, and possibly shed light on the aetiological role of cytokines in accelerating, and probably delaying, an aged phenotype in the CNS of higher species, including humans.

Inflammation and dementia: The associative evidence for a role of inflammation in conditions that impair cognition is strong. In terms of volume, a large amount of cognitive research has been focused on the dementias, particularly Alzheimer's Disease (AD), Lewy Body Dementia (LBD) and the Fronto-Temporal Dementias (FTDs). In such cases it has consistently been demonstrated that the overall inflammatory status of sufferers, including baseline surveillance settings, modulatory dynamics and the acute resolution time scales of cytokines, is altered in a pro-inflammatory direction [18,49]. Nevertheless, unlike the clear temporal relationship between inflammation and onset in delirium, the precise role of various components of the inflammatory constellation, particularly cytokines, in the aetiological triggering and the ongoing pathogenesis of AD is not so clear. At present, it is not entirely certain whether the elevated CSF and peripheral blood cytokine levels frequently found in AD and LBD are a reactive inflammatory response to the disease itself or a causative factor, or both. However, recent work indicates that inflammatory cells and chemokines are involved both aetiologically and reactively in a number of chronic CNS diseases, including those associated with ageing such as AD, LBD, FTDs and Parkinson's Disease (PD) [21].

Inflammation and other forms of neuronal dysfunction: Other neurological functions are altered by a pro-inflammatory milieux, and many of these are either more prevalent in older age or their clinical impact is greater in that age group. For example, autonomic down-regulation, such as the reduction or loss of vagal tone, that is often observed clinically after lower respiratory tract infections, pyelonephritis and other infections, appears to be at least partly mediated by IL-1 and TNF via receptors located on autonomic neurons [75], though other deconditioning pathways are thought to be involved [77]. Similarly, and probably involving the same types of cytokine receptors [77], the down-regulation of cardiovascular sympathetic reflexes contributes to orthostatic hypotension, which can lead to fainting and falls especially in older patients after acute inflammatory illnesses. It can be argued that mechanisms of the same type are likely to be involved in the pathogenesis of the persistent autonomic dysfunction associated with chronic inflammatory conditions such as RA [78]. Less empirical evidence has been generated about the contribution of inflammation chemistry to dysfunction in sensory, motor and extrapyramidal systems, and it is noteworthy in the context of this paper that all these neuropathological domains tend to have a rising incidence with age, apart from a number of relatively uncommon neuro-inflammatory conditions seen mainly in younger people, and diseases with an inherited aetiology.

Indirect mechanisms- mainly vascular: Not all the detrimental influence of inflammation on CNS function is direct. Cognitive decline is also associated with cerebrovascular disease. When cognitive decline is a consequence of the arterial disease itself this is sometimes referred to as vascular dementia (VAD) which is now also known to have complex inflammatory mechanisms involved in its pathogenesis and is another CNS disease state that is broadly associated with older age [79]. Interestingly, VAD and AD share a number of long-term risk factors, such as T2DM, appear to have similar inflammatory chemical profiles and not uncommonly co-exist, so it has been suggested that some of the pathogenic mechanisms are likely to be similar [79]. Low-level chronic elevation of CRP and other acute phase proteins, which are predominantly of hepatocytic origin in response to elevated IL-1, IL-6 and TNF, appears to increase the risk of vascular disease [36,80]. Contextually, as a pathogenic marker CRP can be seen as a flagging molecule for the raised pro-inflammatory cytokines that are more directly active in the pathogenesis of vascular disease, and hence cerebrovascular disease, both directly at endothelial level and by promoting insulin resistance, dyslipidemia and immune cell, mainly macrophage, activity [1]. Empirical research has shown that IL-1, IL-6 and TNF are consistently associated with such metabolic vectors of vascular pathology [1,10,12]. These findings, taken together with the demonstration of the trans-BBB action of inflammatory cytokines begin to lay the first foundation blocks of a more unified view of the role of inflammation in CNS and other neuronal pathology, and how those factors tie with ageing mechanisms.

Dealing with complexity: A proposed alternative approach to inflammation dynamics

In the paragraphs above an overview has been presented of some of the currently known relationships between inflammation, ageing, immune modulation and certain aspects of neuropathology. The examples are drawn from work involving a relatively narrow, but extensively researched, set of immune

system biochemicals such as the cytokines IL-1, IL-6, TNF and IL-10. However, a large number of more recently identified cytokines and other biochemicals take part in cell to cell communication not only within the scope of the innate and adaptive immune systems but also many other aspects of whole-organism reactive and homeostatic functions that are dependent upon immune system influences. The list is extensive and does not need to be presented in its entirety in this paper, but includes chemokines of all classes, such as interleukins, various other cytokines and interferons, as well as cortisol and other steroids, catecholamines, some other hormones and, perhaps more obliquely, endorphins and neurotransmitters. Add to this the membrane and/or intracellular receptors for such signalling molecules, the epigenetic control systems that govern the synthesis of the signalling entities and their receptors, nutritional factors, and the intracellular and extracellular inorganic ionic environment, and it is plainly obvious that the system is immensely complex, and very difficult to envisage, describe or predict. Nevertheless, immune system function is highly effective across many species and remains stable in most individuals for most of their life with only subtle deteriorative changes in old age, so logic dictates it must be physiologically robust and ought therefore to be describable and predictable providing it is well enough understood. The inevitably reductive methods that are demanded by empirical research in biochemistry and molecular biology tend to encourage researchers to present their work in terms of linear reactions, and to illustrate them, usually for the purpose of publication, in one or two dimensions. Indeed, for most scientists, that is the style of early learning in the field of chemistry. However, in the biological reality of live cells and whole organisms there exists a much more complex, inter-dependent, multi-dimensional and dynamic but highly regulated chemical environment. This demands a far more sophisticated means of description and analysis if it is to be properly understood and for its responses to perturbations, such as drugs, infection and deficiency states to be modelled and anticipated. In visual and analytic terms, it is tempting for this to be represented as an interconnecting web in two or three dimensions [81] with corresponding descriptors for the nodal points, connecting strands and tensions representing various aspects of the system. While aesthetically attractive, such an approach is barely a step forward toward a real grasp of biological system complexity as it is virtually impossible in such a model to account for important variables such as time, age, temperature, rates of change, pH etcetera, or to anticipate emergent properties and behaviours. Such a model is limited by the need to fix the co-ordinates of ascribed characteristics rather than allow fluidity of assignment. To make real progress the author proposes that computed multi-variable multi-dimensional analysis is required, possibly using a conditional logic system such as Boolean modelling, though even that has proved to be elusive beyond a certain level of complexity [82,83].

Conclusion

If application software can be developed to a sufficient level of resolution, such an approach could have sufficient power take account of the large number of inter-dependent and changing variables that are characteristic of biological control systems, not only statically but also in modelled and actual real time. Such an approach could begin to illuminate an understanding of immune system control and guide the way to a more complete, and ultimately a more utilitarian, view of the role of immune systems in, for example, immunity itself, vaccine biology, some aspects of oncology, ageing and complex clinically important age-related neurological conditions such as delirium, dementia and Parkinson's disease. It might also have a predictive role in determining the risk of and outcomes of immune dysfunction patterns that are particularly related to ageing, such as chronically raised low-amplitude systemic inflammation, slowly resolving post-acute inflammation, reduced integrity of immune surveillance and the complete breakdown of inflammatory regulation that results in cytokine storm reactions. Only collaboration between clinicians, biologists, mathematicians and software engineers will take this issue forward. The opportunities for research in this domain are therefore exciting and extensive.

REFERENCES

1. Chung HY, Kim DH, Lee EK, Chung KW, Chung S, Lee B, et al. Redefining chronic inflammation in aging and age-related diseases: proposal of the senoinflammation concept. Aging Dis. 2019;10(2): 367-382.
2. Allen SC (2017) Systemic inflammation in the genesis of frailty and sarcopenia: an overview of the preventative and therapeutic role of exercise and the potential for drug treatments. Geriatrics. 2017;2(1): 6.
3. Cunningham C, Hennessy E. Co-morbidity and systemic inflammation as drivers of cognitive decline: new experimental models adopting a broader paradigm in dementia research. BMC Alzheimer's Res Ther. 2015;7: 33.
4. Trzapacz PT, Franco JG, Meagher DJ, Lee Y, Kim JL et al. (2018) Delirium phenotypes by age and sex in a pooled data set of adult patients. J Neuropsych Clin Neurosci. 2018;30(4): 284-301.
5. Kimbrell DA, Beutler B.The evolution and genetics of innate immunity. Nat Rev Genet. 2001;2(4): 256-267.
6. Colaco HG, Moita LF. Initiation of innate immune responses by surveillance of homeostatic perturbations. FEBS Journal. 2016;283(13): 2448-2457.
7. Fulop T, Larbi A, Dupuis G, Le Page A, Frost EH, Cohen AA, et al. Immunosenescence and inflamm-aging as two sides of the same coin: friends or foes? Front Immunol. 2018;8: 1960.
8. Woods JA, Wilund KR, Martin SA, Kistler BM. Exercise, inflammation and aging. Aging Dis. 2012;3(1): 130-140.
9. Bruunsgaard H, Pedersen BK. Age-related inflammatory cytokines and disease. Immunol. Allergy Clin N Am. 2003;23(1): 15-39.
10. Franceschi C, Campisi J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. J Gerontol A Biol Sci Med Sci. 2014;69: S4-S9.
11. Wener MH, Daum PR, McQuillan GM. The influence of age, sex and race on the upper reference limit of serum C-reactive protein concentration. J Rheumatol. 2000;27(10): 2351-2359.
12. Chung HY, Cesari M, Anton S, Marzetti E, Giovanni S, et al. Molecular inflammation: underpinnings of aging and age-related diseases. Ageing Res Rev. 2009;8(1): 18-30.
13. Caspersen CJ, Pereira MA, Curran KM. Changes in physical activity patterns in the United States, by sex and cross-sectional age. Med Sci Sports Exerc. 2000;32(9): 1601-1609.

14. Ellula MS, Pitimak I, Khaza'ai H, Rahmat A, Abed Y.Obesity and inflammation: the linking mechanism and the complications. Arch Med Sci. 2017;13(4): 851-853.
15. Cowie CC, Rust KF, Byrd-Holt DD, Eberhardt MS, Flegal KM, Engelgau MM, et al. Prevalence of diabetes and impaired fasting glucose in adults in the US population: NHANES survey 1999–2002. Diabet Care. 2006;29(6): 1263-1268.
16. Starr ME, Saito H. Sepsis in old age: Review of human and animal studies. Aging Dis. 2014;5(2): 126-136.
17. Sendama W. The effect of ageing on the resolution of inflammation. Ageing Res Rev. 2020;57: 101000.
18. Kalaria RN, Maestre GE, Arizaga, Friedland RP, Galasko D, Hall K, et al. Alzheimer's disease and vascular dementia in developing countries: Prevalence, management, and risk factors. Lancet Neurol. 2008;7(9): 812-826.
19. Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, et al. Prevalence of chronic kidney disease in the United States. JAMA. 2007;298(17): 2038-2047.
20. Dagenais S, Garbedian S, Wai EK. Systematic review of the prevalence of radiographic primary hip osteoarthritis. Clin Orthop Relat Res. 2009;467(3): 623-637.
21. Skaper SD, Facci L, Zusso M, Giusti P. An inflammation-centric view of neurological disease: beyond the neuron. Front Cell Neurosci. 2018;12: 72.
22. Stojkovska I, Wagner BM, Morrison BE.Parkinson's disease and enhanced inflammatory response. Exp Biol Med. 2015;240(11): 1387-1395.
23. Ballou SP, Lozanski FB, Hodder S, Rzewnicki DL, Mion LC, Sipe JD, et al. Quantitative and qualitative alterations of acute-phase proteins in healthy elderly persons. Age Ageing. 1996;25(3): 224-230.
24. Ershler WB, Sun WH, Binkley N, Gravenstein S, Volk MJ, Klopp RG, et al. Interleukin-6 and aging: Blood levels and mononuclear cell production increase with advancing age and in vitro production is modifiable by dietary restriction. Lymphokine Cytokine Res. 1993;12(4): 225-230.
25. Wei J, Xu H, Davies JL, Hemmings GP. Increase in plasma IL-6 concentration with age in healthy subjects. Life Sci. 1992;51(25): 1953-1956.
26. De Gonzalo-Calvo D, Neitzert K, Fernández M, Vega-Naredo I, Caballero B, Garcia-Marcia M, et al. Differential inflammatory responses in aging and disease: TNF-α and IL-6 as possible biomarkers. Free Rad Biol Med. 2010;49(5): 733-737.
27. Ahluwalia N, Mastro AM, Ball R, Miles MP, Rajendra R, Handte G. Cytokine production by stimulated mononuclear cells did not change with aging in apparently healthy, well-nourished women. Mech Ageing Dev. 2001;122: 1269-1279.
28. Beharka AA, Meydani M, Wu DL, Leka S, Meydani A, Meydani SN. Interleukin-6 production does not increase with age. J Gerontol A Biol Sci Med Sci. 2001;56(2): 81-88.
29. Kabagambe EK, Judd SE, Howard VJ, Zakai NA, Jenny NS, Hsieh M, et al.Inflammation biomarkers and risk of all-cause mortality in the RCARDS cohort. Am J Epidemiol. 2011;174(3): 284-292.
30. DeMartinis M, Franceschi C, Monti D, Ginaldi L. Inflammation markers predicting frailty and mortality in the elderly. Exp Mol Pathol. 2006;80(3): 219-227.
31. Dalle S, Rossmeislova L, Koppo K. The role of inflammation in age-related sarcopenia. Front Physiol. 2017;8: 1045.
32. Penninx BW, Kritchevsky SB, Newman AB, Nicklas BJ, Simonsick EM, Rubin S, et al. Inflammatory markers and incident mobility limitation in the elderly. J Am Geriatr Soc. 2004;52(7): 1105-1113.
33. Christian LM, Glaser R, Porter K, Malarkey WB, Beversdorf D, Kiecolt-Glaser J. Poorer self-related health is associated with elevated inflammatory markers among older adults. Psychoneuroendocrinology. 2011;36(10): 1495-1504.
34. Cerejeira J, Lagarto L, Mukaetova-Ladinska EB. The immunology of delirium. Neuroimmunomodulation. 2014;21(2): 72-78.
35. Michaud M, Balardy L, Moulis G, Gaudin C, Peyrot C, Vellas B, et al. Proinflammatory cytokines, aging, and age-related diseases. J Am Med Dir Assoc. 2013;14(12): 877-882.
36. Golbidi S, Laher I. Exercise and the aging endothelium. J. Diabetes Res. 2013;2013: 789607.
37. Shao Y, Saredy J, Yang WY, Sun Y, Lu Y, Saaoud F, et al. Vascular endothelial cells and innate immunity. Arterioscler Thromb Vasc Biol. 2020;40(6): e138-e152.
38. Bruunsgaard H, Skinhoj P, Qvist J, Pedersen BK. Elderly humans show prolonged in vivo inflammatory activity during pneumococcal infections. J Infect Dis. 1999;180(2): 551-554.
39. Krabbe KS, Bruunsgaard H, Hansen CM, MøllerK, Fonsmark L, Qvist J, et al. Ageing is associated with a prolonged fever in human endotoxemia. Clin Diagn Lab Immunol. 2001;8(2): 333-338.
40. Chung HY, Kim DH, Lee EK, Chung KW, Chung S, Lee B, et al. Redefining chronic inflammation in aging and age-related diseases: proposal of the senoinflammation concept. Aging Dis. 2019;10(2): 367-382.
41. Ohman H, Savikko N, Strandberg TE, Pitkälä KH. Effect of physical exercise on cognitive performance in older adults with mild cognitive impairment or dementia: a systematic review. Dement Geriatr Cogn Disord. 2014;38(5): 347-365.
42. Lee SS, Lo Y, Verghese J. Physical activity and risk of postoperative delirium. J Am Geriatr Soc. 2019;67(11): 2260-2266.
43. Gual N, Garcia-Salmones M, Britez L, Crespo N, Udina C, Perez LM, et al. The role of physical exercise and rehabilitation in delirium. Eur Geriatr Med. 2020;11: 83-93.
44. Tanaka T, Narazaki M, Kishimoto T (2014) Interleukin-6 in inflammation, immunity and disease. Cold Spring Harb Perspect Biol. 2014;6(10): a016295.
45. Peçanha T, Lima RAH. Inflammation and cardiovascular autonomic dysfunction in rheumatoid arthritis: a bidirectional pathway leading to cardiovascular disease. J Physiol. 2017;595(4): 1025-1026.
46. Scheller J, Chalaris A, Shmidt-Arras D, Rose-John S. The pro- and anti-inflammatory properties of the cytokine interleukin-6. Biochim Biophys Acta. 2011;1813(5): 878-888.
47. Pal M, Febbraio MA, Whitham M. From cytokine to myokine: The emerging role of interleukin-6 in metabolic regulation. Immunol Cell Biol. 2014;92(4): 331-339.
48. Han MS, White A, Perry RJ, Camporez JP, Hildago J, Shulman GI, et al. Regulation of adipose tissue inflammation by interleukin 6. Proc Natl Acad Sci USA. 2020;117(6): 2751-2760.
49. Zotova E, Nicoll JAR, Kalaria, Holmes C, Boche D. Inflammation in Alzheimer's disease: relevance to pathogenesis and therapy. Alzheimers Res Ther. 2010;2(1): 1-3.
50. Mikkelsen UR, Couppe C, Karlsen A, Grosset JF, Schjerling P, Mackey AL, et al. Life-long endurance exercise in humans: Circulating levels of inflammatory markers and leg muscle size. Mech Ageing Dev. 2013;134(11): 531-540.
51. Pedersen BK, Steensberg A, Fischer C, Keller C, Keller P, Plomgaard P, et al.Searching for the exercise factor: Is IL-6 a candidate? J Muscle Res Cell Motil. 2003;24: 113–119.
52. Pedersen AMW, Pedersen BK. The anti-inflammatory effect of exercise. J Appl Physiol. 2005;98(4): 1154–1162.
53. Pedersen BK, Steensberg A, Fischer C, Keller C, Ostrowski K, Schjerling P. Exercise and cytokines with particular focus on muscle-derived IL-6. Exerc Immunol Rev. 2001;7: 18-31.

54. Fischer CP. Interleukin-6 in acute exercise and training; what is the biological relevance? Exerc Immunol Rev. 2006;12: 6-33.
55. Fiser WM, Hays NP, Rogers SC, Kajkenova O, Williams AE. Evans CM, et al. Energetics of walking in elderly people: factors related to gait speed. J Gerontol A Biol Sci Med Sci. 2010;65(12): 1332-1337.
56. Niklas BJ, Brinkley TE. Exercise training as a treatment for chronic inflammation in the elderly. Exerc Sport Sci Rev. 2009;37(4): 165-170.
57. Woods JA, Veira, VJ, Keylock KT. Exercise, inflammation and innate immunity. Immunol Allergy Clin North Am. 2009;29(2): 381-393.
58. Pedersen BK. Exercise-induced myokines and their role in chronic disease. Brain Behav Immun. 2011;25(5): 811-816.
59. Brandt C, Pedersen BK. The role of exercise-induced myokines in muscle homeostasis and the defence against chronic diseases. J Biomed Biotechnol. 2010;2010: 520258.
60. Narici MV, Maffulli N. Sarcopenia: Characteristics, mechanisms and functional significance. Br Med Bull. 2010;95: 139-159.
61. Leeuwenburgh C. Role of apoptosis in sarcopenia. J Gerontol A Biol Sci Med Sci. 2003;58(11): 999-1001.
62. Demontis F, Rosanna P, Goldberg AL, Perrimon N. Mechanisms of skeletal muscle aging: insights from Drosophila and mammalian models. Dis Model Mech. 2013;6(6): 1339-1352.
63. Walrand S, Guillet C, Salles J, Cano N, Boirie Y. Physiopathological mechanism of sarcopenia. Clin Geriatr Med. 2011;27(3): 365-385.
64. Pedersen BK, Febbraio M. Muscle-derived interleukin-6: a possible link between skeletal muscle, adipose tissue, liver and brain. Brain Behav Immun. 2005;19(5): 371-376.
65. Iuliano E, di Cagno A, Cristofano A, Angiolillo A, D'Aversa R, Ciccotelli S, et al. Physical exercise for prevention of dementia (EPD) study: background design and methods. BMC Public Health. 2019;19: 659.
66. Kishimoto T. IL-6: From its discovery to clinical applications. Int Immunol. 2010;22(5): 347–352.
67. Alam A, Hana Z, Jin Z, Suen KC, Ma D. Surgery, neuroinflammation and cognitive impairment. EBioMedicine. 2018;37: 547-556.
68. Westhoff D, Witlox J, Koenderman L, Kalisvaart KJ, de Jonghe JFM, sTIJN mfn, et al. Preoperative cerebrospinal fluid cytokine levels and the risk of postoperative delirium in elderly hip fracture patients. J Neuroinflammation. 2013;10: 122.
69. Vasunilashorn SM, Ngo L, Inouye SK, Libermann TA, Jones RN, Alsop DC, et al. Cytokines and postoperative delirium in older patients undergoing major elective surgery. J Gerontol A Biol Sci Med Sci. 2015;70(10): 1289-1295.
70. van Gool WA, van de Beek D, Eikelenboom P. Systemic infection and delirium: when cytokines and acetylcholine collide. Lancet. 2010;375(9716): 773-775.
71. Allison DJ, Ditor DS. The common inflammatory etiology of depression and cognitive impairment: a therapeutic target. J Neuroinflammation. 2014;11: 151.
72. Simone MJ, Tan ZS. The role of inflammation in the pathogenesis of delirium. CNS Neurosci Ther. 2011;17(5): 506-513.
73. Pan W, Stone KP, Hsuchou H, Manda VK, Zhang Y, kastin AJ. Cytokine signaling modulates blood-brain barrier function. Curr Pharm Des. 2011;17(33): 3729-3740.
74. Erickson MA, Banks WA. Age-associated changes in the immune system and blood-brain barrier functions. Int J Mol Sci. 2019;20(7): 1632.
75. Probert L. TNF and its receptors in the CNS: the essential, the desirable and the deleterious effects. Neuroscience. 2015;302: 2-22.
76. Tajes M, Ramos-Fernandez E, Weng-Jiang X, Bosch-Morato M, Guivernan B, Eraso-Pichot A, et al. The blood-brain barrier: structure, function and therapeutic approaches to cross it. Molec Membr Biol. 2014;31(5): 152-167.
77. Tizard I. Sickness behaviour, its mechanisms and significance. Anim Health Res Rev. 2008;9(1): 87-99.
78. Sandhu V, Allen SC. The effects of age, seropositivity and disease duration on autonomic cardiovascular reflexes in patients with rheumatoid arthritis. Int J Clin Pract. 2004;58(8): 740-745.
79. Venkat P, Chopp M, Chen J. Models and mechanisms of vascular dementia. Exp Neurol. 2015;272: 97-108.
80. Johnson DB, Kip KE, Marroquin OC, Ridker PM, Kelsey SF, sHAW lj, et al. Serum amyloid A as a predictor of coronary artery disease and cardiovascular outcome in women: the National Heart, Lung, and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE). Circulation. 2004;109(6): 726-732.
81. Stobbe MD, Jansen GA, Moerland PD, van Kampen AHC. Knowledge representation in metabolic pathway databases. Brief Bioinfo. 2012;15(3): 455-470.
82. Liu R, Qian C, Liu S, Jin Y-F. State feedback control design for Boolean networks BMC Syst Biol. 2016;10: 70.
83. Layek RK, Datta A, Dougherty ER. From biological pathways to regulatory networks. Mol BioSyst. 2011;7(3): 843-851.