

BIOCHEMICAL DETERMINANTS OF AGGRESSIVE BEHAVIOUR – PATHO-PHYSIOLOGICAL CONNECTIONS IN ESRD AND DIALYSIS

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Abstract

Violence and aggression are among the most important problems of the contemporary world. Modern humanity vices, like alcohol, drug abuse, daily stress, but also specific therapies within the positive tendency to prolong life in severe chronic diseases seems to contribute to the ascending trend of aggressive behaviour. A topic of debate is the ability of chronic kidney disease and its treatment to induce biochemical and behavioural changes that predispose to impulsivity. The answer can reveal treatment adjustments (chemical, procedural and psychological) that can be made for improving behavioural condition and the quality of life in these patients.

Rezumat

Violența și tendința la agresivitate reprezintă unele dintre cele mai importante probleme cu care se confruntă societatea contemporană. Amploarea în creștere a fenomenului pare a fi determinată nu numai de viciile lumii moderne (abuzul de alcool și droguri, stresul cotidian), ci și de efectele anumitor terapii menite a prelungi durata de viață în afecțiuni severe infirmizante. Un subiect actual de dezbateră este reprezentat de influența bolii cronice de rinichi și a tratamentului prin hemodializă asupra bazelor biochimice ale agresivității. Elucidarea mecanismelor prin care această afecțiune ar putea favoriza (la nivel chimic, procedural sau psihologic) tendințele impulsive ale individului ar permite modificări terapeutice care să amelioreze problemele comportamentale și calitatea vieții pacientului.

Keywords: aggression, biochemical mediators, chronic kidney disease, haemodialysis

Introduction

Violence and aggression are among the most important problems of the contemporary world, with uprising prevalence and worsening consequences [1]. Not only modern humanity conditions and addictions, like alcohol, drug abuse and increasing daily stress, but also the positive tendency to prolong life in severe chronic diseases seem to contribute to this proven ascending trend of aggressive behaviour [2, 3]. In the recent years, an increasing number of violent manifestations were reported among patients with disabling chronic diseases, namely oncology patients, those with HIV/AIDS and patients on maintenance haemodialysis treatment (associating or not diabetes mellitus) [4-6]. Impulsive and aggressive actions are

reported with increased prevalence in chronic dialysis centres [7-10].

This alarming phenomenon induced several complex analyses regarding the factors that induce and influence violence [11, 12]. A topic of debate is the ability of chronic kidney disease and its treatment to induce biochemical and behavioural changes that predispose to impulsivity. The answer can reveal us treatment adjustments (chemical, procedural and psychological) that can be made for improving this condition, along with increasing the quality of life of these patients.

Determinants of aggression

The determinants of the hostile and aggressive behaviour are genetic, endocrine, biochemical and

social [2, 13]. As the genetic and social factors are mostly non-biased, to focus on the biochemical and endocrine components of the aggression complex.

The cerebral region that integrates neurohumoral circuits is amygdala, its hyperactivity being responsible for upraising aggressive tendencies [14]. Changes in brain function can be induced by several hormones and other substances which modulate cerebral centres activity. End stage renal disease (ESRD) and dialysis as the most common treatment modality of our days for this condition seem to influence neurotransmitters involved in the process.

Biochemical components involved in modulating the impulsive behaviour - specific changes in chronic dialysis patients

Serotonin (5-Hydroxytryptamine 5-HT) is secreted by specific cells in gastrointestinal tract and serotonergic neurons of central nervous system, but also in renal proximal tubules, as MJ Sole *et al.* demonstrated in interesting studies on male Wistar rats in 1986 [15-17]. 5-HT can be found in circulating platelets and here the uptake, deposit and release resembles the brain serotonin physiology [16, 17]. Known to modulate the prefrontal activity by stimulating serotonin 5HT₂ receptors in orbital frontal and anterior cingulate cortex, serotonin acts as a local neurotransmitter and paracrine modulator of brain circuits [18, 19]. Low serotonergic activity predisposes to aggression; Murphy *et al.*, 2002 in studies on human healthy volunteers and De Boer, 2009 on laboratory-bred rats and mice revealed that serotonin and/or the precursor tryptophan deficiency can rise suicidal and violence risks [20, 21]. Serotonin release allows the person to manage unpleasant events with calm and inhibits aggressive actions dictated by genetic features [2, 21].

Barisc and Pivac in 2004 demonstrated, in a case-control study including dialysis patients with depressive symptoms (with and without anxiety) *versus* non-renal patients diagnosed with depression, that serotonin content in platelets is lower in all dialysis patients, but significantly higher in dialysis patients with anxiety compared with depressive individuals. Based on previous studies, and confirmed by recent works, they motivated that low serotonin in ESRD patients is due to low concentration of plasma tryptophan and altered 5-HT synthesis, as well as to the impaired peripheral serotonin uptake determined by the influence of haemodialysis procedure upon platelets; the authors concluded that platelet serotonin content should be further assessed as a marker for anxiety in chronic dialysis patients [22, 23]. A comprehensive review of Hedayati in 2012 showed that anxiety is a feature of depressive patients and serotonin-selective reuptake inhibitors (SSRIs) used in dialysis patients ameliorate the depression-associated impulsivity, but only a few of the class's representatives are well tolerated

(fluoxetine with no dose adjustment; paroxetine, with dose adjustment; sertraline may increase the risk of bleeding after dialysis sessions) [24].

Testosterone. While serotonin can counteract the aggressive impulses, testosterone excess exerts an opposite effect: it promotes impulsivity and violent behaviour in animals [25]. Intensively studied, this rule is uncertain in humans. Testosterone level is low in chronic dialysis males and should have protective effects against the aggressive behaviour, but this is not the case in real practice [26]. The explanation came later, with the contribution of the studies performed by Coccaro in 2017 and Mehta *et al* in 2010, highlighted by the documented review of Montoya in 2012, establishing that testosterone high levels trigger aggression only when they coexist with low plasmatic cortisol [27-29].

Cortisol, produced by the *zona fasciculata* in the adrenal cortex and released in response to stress and hypoglycaemia, was accordingly named "the stress hormone" [30-32]. In relation to impulsivity, cortisol reduces amygdala-mediated anger processing, in opposition with testosterone actions, promoting fear reactions [33].

There are numerous studies revealing the heterogeneous distribution of cortisol levels in chronic dialysis patients. Chinese studies on large cohorts demonstrated that corticoid activity is negatively associated with the glomerular filtration rates, and positively with serum creatinine, as its levels continuously increase with the progression of chronic kidney disease [34]. Other studies found low cortisol levels in haemodialysis patients, but significantly high levels of cortisol metabolites (tetrahydrocortisol, 5 α -tetrahydrocortisol and tetrahydrocortisone) with toxic effects; high cortisol levels in end stage renal disease were associated with inflammation and increased mortality risk [35-38]. It is certain that the sustained treatment of any inflammatory trigger, the preservation of a healthy vascular access and a good nutrition status without hypoglycaemic events can contribute to maintain normal cortisol levels in dialysis population and ameliorates cardiovascular risks [39]. Cortisol and cortisol metabolites implications in neurohumoral status of chronic renal patients remain subjects for further investigations.

Catecholamines, dopamine and norepinephrine, act by enhancing the predisposition for other directed aggressions [40]. An increased noradrenergic receptors stimulation (e.g. by the alpha agonist clonidine, widely used for hypertension treatment in dialysis) is correlated with irritability [41]. Beta-blockers seem to be effective in reducing aggressive behaviour in patients with brain lesions [42].

Norepinephrine levels are increased in dialysis patients, especially in anuric patients [43, 44]. Sympathetic over activity in these patients contributes to the aetiology of hypertension, cardiac arrhythmia and severe cardio-

vascular events and must be counteracted by beta-adrenergic antagonists. Yet, the influence of beta-blockers on aggressive behaviour in dialysis subjects remains to be assessed. Some authors recommend the use of beta-blockers in episodic anxiety of dialysis patients [45]. Brazilian studies found a negative correlation between the beta-blockers use and the anxiety manifestations in haemodialysis patients; furthermore, pindolol was found as a successful antidepressant enhancer in these patients [46].

Gamma-aminobutyric acid (GABA) is also implicated in the aggression mechanisms [47]. Reduced activity of GABA receptors type A and glutamatergic enhancement are associated with aggressive behaviour [2, 48]. Uraemia is known to reduce the brain GABA release, uptake and degradation, with a simultaneously increase of glutamate levels. It is suggested by some studies that the use of gabapentin can ameliorate high blood pressure levels and psychotic disorders in uremic patients [47]. Haemodialysis reduces the circulating glutamate excess [49, 50], but there are no studies to reveal if prolonged dialysis sessions can reduce impulsivity in ESRD patients.

A recent study in chronic dialysis patients connects low levels of parathyroid hormone (iPTH) with anxiety [51]. In relation to this finding, reductions in active vitamin D levels, a common feature of ESRD patients due to the lack of renal hydroxylation, are linked with increased risks of antisocial and impulsive behaviour [52]. The mechanism involves the influence of cholecalciferol on the expression of tryptophan hydroxylase2 (TPH2), an enzyme responsible for serotonin synthesis [53]. The connection between vitamin D levels and serotonin effects was approached by several studies and it seems to be a subject of serious debate which deserves to be further investigated [54, 55]. Positive results can open new horizons in the management of dialysis patients, as a more serious therapeutic approach of renal mineral and bone disorder can be proved to ameliorate also depression and anxiety tendencies in this population. Native Vitamin D supplements starting from the early chronic kidney disease stages, active vitamin D or vitamin D receptor activators in late stages, the association of calcimimetics in the presence of hypercalcaemic secondary hyperparathyroidism are possible ways to approach this complex issue [55].

As the above mentioned studies have shown, all the substances involved in modulating the behaviour tendencies suffer important variations in maintenance dialysis patients. These biochemical perturbations overlap with many psychological factors affecting this group of patients [56]. Nevertheless, the exhaustive analysis of all found studies regarding neurotransmitters involved in aggression and the influence of dialysis treatment on their levels are, still, topics of debate. More research is needed for determining the real impact of genetic/biochemical/psychological and social in

triggering violent reactions and aggressive behaviour acts.

Conclusions

There are numerous substances involved in generating aggressive tendencies in humans. Their disturbed levels are linked with brain receptors disruptions determining depression in aggressive behaviour. End-stage renal disease has a major negative impact on patient's physical and psychological status and the dialysis procedure itself is demanding, requiring major lifestyle changes and producing psychological distress. On the other hand, toxins accumulation in chronic renal failure and their heterogeneous excretion by dialysis may cause imbalances in hormones favouring/inhibiting aggressive behaviour. Focusing on biochemical transformations during chronic kidney disease progression, superposed on the humoral and psychosomatic changes produced by the maintenance haemodialysis treatment, the study of aggressive and violent pattern in chronic dialysis patients can bring a light on this subject.

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