Apathy: Negative Symptoms after Stroke, Independent of Depression

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Abstract: Neurological disorders cause a number of both mood and motivation problems, as well neuropsychological deficits. Apathy is a major clinical sequelea seen after stroke. Patients with stroke patients have features of depression, and motivation impairment (apathy). Apathy is a reduction in initiating cognitive, emotional and behavioural responses. Patients have lower motivation in many psychological domains. Therefore, apathy is proposed here as "negative symptom" of stroke. Apathy is a prevalent clinical presentation and causes problems to caregiver and rehab teams. The pathophysiology and neuroanatomy is not specific but detectable. It needs a special approach in understanding as well as treatment and rehabilitation. Apathy is a good predictor of outcome in rehabilitation. The treatment is a multidisciplinary and needs deferent management from depression. Here we raise clinical awareness and encourage Clinicians and researchers address apathy as it has significant recovery impact.

Keywords: Stroke, Brain disease, Apathy, Depression, Rehab, Neuropsychology.

INTRODUCTION

Neuropsychological disorders, as well as mood and motivation disorders are common consequences of brain disease and injuries. This includes both traumatic (such as TBI) as well as non-traumatic injury, *.e.g*. stroke, and tumour [1, 2].

It has been widely accepted now that stroke is a major public health problem in the USA, and globally; every year about 795 000 people in the USA alone have a stroke [3]. Of the 15-millions people worldwide who suffer a stroke annually, at least 5 million are permanently disabled, placing a burden on family and community [1, 3]. Depression and apathy are very common features of post stroke clinical presentations [1, 2]. Apathy is an important clinical problem effects the outcome of treatment and rehab [4]. Apathy is both common symptoms and ignored clinical problem of chronic neurological diseases [2]. This paper will address the problem of apathy in relation to mainly stroke, but other neurological disorders are also indicated. The aim is to explain the symptoms and its relations to other clinical manifestations following stroke.

Apathy can be seen in many disorders, such as TBI, CVA, AD, Parkinson's disease [2, 5]. Therefore, there is no specificity of apathy related to a given brain disorder. It can be argued, therefore, that apathy is a symptom, not a syndrome, related to a number of brain disorders. While other researchers suggest that apathy is a syndrome post stroke [1].

Apathy

Apathy has been linked to brain disease from the ancient Greek times, the word pathos or passions [7], therefore apathy means lack of interest and lower motivation. Apathy is not attributed to a diminished level of consciousness, cognitive impairment or emotional distress, but impaired motivation [8]. But the concept "boul" means will and aboulia means lack of a will, in Greek. When patients show physiological and psychological non-reactivity [9] they are considered to have apathy. Behavioural approaches consider operational definition and classification [9] suggest that apathy is "characterised by diminished goal-directed behaviour, diminished goal-directed cognition, and decreased emotional concomitants of goal directed behaviour". It is interesting to see here inclusive definition, to account for behaviour, cognition and emotion. The salient point here of course is the 'decreased' level of output.

But another domain that seems to be missing in definition and discussions is the lack of awareness. This may also be included in both definition and assessments. Patients with neurological diseases show impaired cognitive, emotional as well as behavioural goal-directed behavior [1]. Cognitively, they show impaired interest in attending or learning new skills. Emotionally, when they are not showing responses of emotional nature to environments around them. Behaviourally, for instance, they show deficits in action in response to stimuli; either targeting them or relevant to the daily activities. Though others [10] have

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considered it as a motivation deficits, there is inconsistency among researchers and clinicians as to the definition yet.

Clearly some researchers think that apathy as "the absence of feeling that frequently occurs together with a lack of emotional sensitivity and flattening of affective response" [9]. From a behavioural perspective, apathy defined as "a behavioural syndrome consisting of a reduction of self-generated voluntary and purposeful behavioural" [9], with a weakness in labelling it "syndrome" since it is not independent of neurological disorders. Clinically, we see patients with deficits in spontaneity of action and reduced initiation too. Hence, motivation is a key feature of the disorder and considered in recent definition including, the emotional, cognitive and behavioural domains [11]. Robert *et al* [6], assert that apathy is a disorder of motivation, but failed to mention the lower output of motivation.

Apathy as such is a diminished motivational output of patients (in many domains –cognitive, behavioural and emotional), that effects their daily activities, quality of life and so on [5, 6], while no physical disability can be accounted for apathy.

Apathy is "Negative Symptoms" of Stroke

All the above suggests that the main feature of apathy is reduction or diminished behavioural output from patients with neurological disease or disorders, such as stroke, AD, or TBI among others. When we look closely at the clinical presentation of apathy among patients with neurological disorders [1, 2] and examine the assessments tools and questions, it clearly circle around the 'output', rather than the ability. Patients show limited or absent output on a number of behavioural, psychological functioning post illness.

Therefore, we propose here to consider 'apathy' as "negative symptoms" following CVA. Other neurological disorders may also cause such abnormality. This short paper attempts to delineate its "negativeness" in a clinical sense, and invite clinicians to consider it as such. This will, it is hoped, help to encourage different approaches in labelling as well as treating. This is in contrast to "positive symptoms" following CVA. Post stroke patients may show positive symptoms such as hemiplegia, dysphagia, anxiety, anger, irritability and depression as emotion. The positive symptoms represent 'increased' output, while "negative symptoms" show 'decreased' output. Here is the proposed difference.

Therefore, apathy needs to be considered as an independent specific clinical presentation with possible different not-yet known pathogeneses and that it requires a specific treatment approaches.

Classification of Apathy

Apathy has not been well addressed [1] and its classification was ignored. No mentioning was there of the term apathy in the International Classification of Diseases (ICD) -10 [12]. The DSM 5 has improved on the previous version, and included apathy on certain disorders apathetic type" is listed as one subtype of "personality change due to a general medical condition" [13].

While there is no an accepted definition of apathy, there are attempts of classification. Some proposed three criteria for diagnoses and classifications: (I) decreased spontaneity in activity and speech; (ii) prolonged latency in responding to queries, directions and other stimuli; and (iii) reduced ability to persist with a task" [see 14, 1].

Clinical presentations show that there are many types and degrees of apathy [1, 2]. Any valid and comprehensive classification has to stem from a valid, reliable definition and comprehensive list of all manifestations. Particularly, it is important that classification to show the "negative" (*i.e*. reduced) features of its clinical presentation, as clinical negative symptoms of stroke (or other neurological diseases).

Apathy and Depression

Apathy and depression are partially overlapping clinical presentations as well as concepts. They share symptoms such as diminished interest in activities and psychomotor retardation. However, cognitive and affective symptoms of depression, such as feelings of worthlessness or guilt and anhedonia [see; 1, 2, 15], are not considered a part of apathy. Apathy can be correlated with items of depression scales, but not with euphoric items [16]. Patients with Parkinson disease, for instance, can show apathy but not depression, while vascular disorder can show depression with no apathy [17].

Studies have also supported a distinction between anhedonia, defined as loss of interest or pleasure, and apathy. In a study using the Beck Depression Inventory and Apathy Scale with Parkinson's disease patients, the best fitting symptom model included separate apathy and anhedonia factors [18]. This finding was

replicated in a study using multiple measures of anhedonia and a measure of apathy that includes scales for the three proposed symptom dimensions (the Lille Apathy Rating Scale) [19].

In both of these studies, a reduction in interest or pleasure was distinct from behavioural symptoms of apathy (*e.g.*, reduced motivation and engagement in activities).

In both anhedonia and depression the fact that there is loss of pleasure (subjective experience) is a distinctive feature from a behavioural deficit in engaging in activities or initiating them [2].

It seems that apathy can be independent, but can be mixed with, depression and anhedonia. Such independence warrants of course an independent clinical consideration as well as research approach.

Multiple studies support further the distinction between the two constructs. For example, one study found that the best fitting model in a confirmatory factor analysis of an apathy and depression symptoms was one which included multiple factors, including separate apathy and dysphoric mood factors [18]. In evaluating both, scales may have similar items and that may present an invalid similarities. But the distinction between apathy and depression is more apparent when informant reported vs. self-reported ratings are used. For example, in a sample of 49 patients with brain damage, self-rated apathy was significantly correlated with clinician-rated depression ($r = 0.48$, $p<.05$), but informant-rated apathy was not ($r = 0.15$, $p>.05$) [20]. Similar results were found in a relatively large mixed neurological and healthy elderly comparison sample (n=107) in which a clinician-rated measure of depression excluding apathy symptoms was used [21]. Though the two studies differ in sample number and aetiologies, but they show similarities.

Apathy and depression differ in their ability to predict conversion to dementia in individuals with mild cognitive impairment [22].

Several studies have shown that apathy has stronger associations with cognitive and functional impairment than depression [23, 24].

Naturally, the distinction between apathy and depression has clinical and treatment implications. Apathy is associated with impaired insight about one's illness and cognitive abilities while depression is associated with greater insight [1, 25].

Apathy and depression have different structural and functional neural correlates [26, 27]. Apathy is associated with lesions to frontal lobe, subcortical areas for instance, but not depression [2, 28, 29]. This also explains in part the variety of apathy (present or absent) among patients with neurological disorders.

Research on localization of brain areas associated with depression in post stroke was controversial, but certain studies found left anterior to be associated [see for a review, [30].

It is worth noting, however, that apathy and depression can occur as comorbidity. It is estimated that nearly have of patients with depression can have apathy, but much less of the apathy patients report depression [1, 2] post stroke.

Apathy Post Stroke

There is significant literature about apathy in different brain diseases. It can be followed after Parkinson's disease [5] ; dementia and AD (6; see above). Here we will consider apathy following CVA.

Not surprisingly, literature also examined apathy following stroke. One study found that a significant number (23%) of patients with stroke had a significant degree of apathy. The apathetic patients were characterized by being older, having a higher frequency of major but not minor depression, having a greater degree of physical and cognitive impairment, and having lesions involving the posterior limb of the internal capsule [9, 10].

Andersson *et al.* Anderson also examined apathy in patients with stroke (n =30), traumatic brain injury (n =27), and hypoxic brain injury (n =13). Apathy was associated with subcortical right hemisphere lesions as well as a decreased score on the active approach oriented coping questionnaire [32]. Patients naturally after CVA show cognitive impairments, at least some of them. But the focus here on the apathy as well as certain cognitive impairments. Ghika-Schmid and Bogousslavsky [33] examined 12 CVA patients with anterior thalamic infarcts. Although the acute period was characterized by perseverative behaviour and anterograde memory retrieval deficit as well as intrusions, naming difficulties and dysarthria within a few months follow-up, the persisting abnormalities included memory dysfunction and apathy. This report as well as other anecdotal reports in the literature suggested that apathy following stroke, particularly

associated with bilateral lesions, and may persist for many years. Another study [2, 28, 29, 34] reported on a patient (20 Left Frontal Thalamus, 40 Basal ganglia, 60 Internal capsule); 80% of patients show effect of apathy.

The only lesion location that was significantly more frequent in patients with apathy compared to the other groups was the posterior arm of the internal capsule. This may reflect the interruption of pallidomesencephalic fibres from the inner pallidum to the pedunculopontine nucleus which in cats and rodents plays an important role in goal-oriented

Locomotion (data from 9) with right intralaminar nuclei infarction of the thalamus with apathy and cognitive deficits persisting for more than 17 years [28, 29].

Lesions studies that have been conducted suggest that lesions of many brain regions, particularly thalamic, frontal, and subcortical, are associated with apathy. These findings suggest that the cortical-basal ganglia-thalamic circuits which have been implicated in the development of depression may also play a role in apathy. The ansalenticularis, which is the main output of the internal pallidum, occupies part of the posterior limb of the internal capsule [34]. This pathway projects to the pedunculopontine nucleus. This structure, located within the mesencephaliclocomotor region in cats and rodents, sends monosynaptic projections to motorneurons in the anterior horn and plays a prominent role in goal-oriented locomotorbehaviour [35].

Other lesion studies have identified apathy as occurring following damage to specific regions, for example, the ventromedial and dorsolateral prefrontal cortex [36].

It is perhaps predictable possibility that the more the lesion near or in the internal parts of the brain (where movements is also relevant there) the more likely there is apathy. But this is not exclusive. As such, frontal lobe and internal capsules and basal ganglia when effected patients are likely to show apathy.

Neuropsychological Perspective

Apathy may have a reciprocal interaction with the setting of the patients. Apathy is related to environmental, psychological, and neurobiological factors. Patients in nursing home units where more staff time is available for patient care has lower rates of apathy than patients on units with fewer and less available staff [37].

The magnitude of correlations between apathy and specific cognitive test scores varies significantly across studies, perhaps reflecting differences among studies in sample size, the range of cognitive and apathy scores in the sample, and the specific measure of apathy used. For example, in one study, two measures of apathy correlated significantly with the Mini Mental Status Examination (MMSE) (r=-.42 and r=-.32) while a third measure of apathy did not (r=-.06) [38].

Apathy is associated with impairment in both basic activities of daily living (ADLs; *e.g*. dressing, eating) and instrumental activities of daily living (IADLs; *e.g*., handling money, managing medications) [39].

Longitudinal and cross-sectional studies have identified a link between apathy and physical health. Apathy ratings obtained at admission to physical rehabilitation programs predict patient outcomes. Patients identified as apathetic at the start of a rehabilitation program are later rated as being less involved or active those programs [40]. These findings are likely consequence of their decreased involvement, those patients show less improvement compared to non-apathetic patients [41].

Patient apathy has been consistently related to caregiver burden, although the magnitude of this relationship has varied greatly across studies [*e.g*., 42-44].

In a meta-analysis of studies of stroke patients, the type of scale used moderated the prevalence estimate of apathy [1], where there is also a variation in prevalence, age and gender too.

MEASURING APATHY

Apathy Evaluation Scale

Apathy Evaluation Scale is one of the often used measure in the field. The Apathy Evaluation Scale (AES) is an 18 item measure of apathy [45]. There are three versions of the AES: a self-report questionnaire version (AES-S), an informant-report questionnaire version (AES-I), and clinician-lead semi-structured interview version (AES-C). Marin and colleagues [45] labelled 6 items on the AES as cognitive (*e.g*. s/he is interested in things; getting things started on his/her own is important to him/her; s/he is interested in having new experiences), 5 items as behavioural (*e.g*. s/he

gets things done during the day; s/he puts little effort into anything; s/she spends time doing things that interest her/him), 2 items as emotional (*i.e*. s/he approaches life with intensity; when something good happens, s/he gets excited) and 3 items as "other" (*i.e*. s/he has an accurate understanding of her/his problems; s/he has initiative; s/he has motivation). The scales as such cover a range of impaired (negative) motivational aspects and self-awareness.

Principal components analyses of the AES have consistently found evidence for a large general component, representing 30-50% of the scale variance [*e.g*., 46, 47]. This factor has been found in all versions of the AES [45] and in different patient groups (*e.g*. dementia, Clarke *et al*., 2007; first episode psychosis, [47]. This general component often includes items from each of the three diagnostic criteria for apathy: cognitive, behavioural, and emotional symptoms.

Lille Apathy Ratings Scale (LARS)

The Lille Apathy Rating Scale (LARS) was developed as a comprehensive measure of apathy [49]. The scale is based on a structured interview. It includes 33 items, divided into nine domains. Responses are scored on a dichotomous scale. It showed good ability to distinguish between depression and apathy.

Other scale have been used for different reason but include apathy as subscales such as Neuropsychiatric Interview (NPI).The Neuropsychiatric Interview (NPI) was originally designed as a measure of psychopathology for use in dementia patients [50].

The overall pictures addressed by scales (mentioned here or otherwise), seem to generate a clinical presentation of behavioural disorders in which a patient shows "negative symptoms" *.i.e*. reduction in motivation on a number of domains. This is clinically evident as well as in research; reduction in behaviour, and learning.

Reduced motivation (in many domains) cause a burden for rehab team as well as caregivers. The fact that a patient with apathy shows reduction in engagement in rehabilitation and learning, is a problem in advancing their rehab progress [1, 2]. As a consequence this will increase the length of hospital stay as well impact the permanency of the CVA-related disability or impairments. Hence, any attention to apathy will improve the rehabilitation process as well as improve the quality of life for patients and caregivers. Not to mention the economic benefit from improving patients' apathy.

The treatment of apathy have shown to be interdisciplinary. Medications have a role to play but also the behavioural management. Pharmacological evidence is inconsistent and there are some case reports of benefiting from dopamine agonist [1], but much research needed. Behavioural approached with reinforcements techniques may also help, and control trials needed. All staff and caregiver have to detect apathy as early as possible and work on treating it, from early manifestation features.

CONCLUSIONS

Apathy is a common clinical disorder following stroke, and other neurological disorders and diseases. Apathy may have, nevertheless, been given less attention in clinical and research work. There is considerable evidence to show that many patients after stroke could show a form apathy in one stage or the other. This reported apathy is an independent of depression, which is also prevalent post stroke. Apathy is proposed here as (negative symptoms) following stroke; negative in the sense of being reduced level of motivation. It is manifested in a reduction in motivation in general, that can be seen in cognition, behaviour, or emotion.

The nature of this negative clinical presentation is a factor in being ignored in clinical management. Since apathy does not effect staff or caregivers and it attracts less attention, unlike positive symptoms, such as angry reaction, aggression or crying and depression. It is also often misdiagnosed as depression, and treated as such with limited benefit. Apathy and depression can be comorbidity, but it argued here as independent symptoms and it is widely agreed now [1, 2]. This small commentary aimed to improve awareness. Apathy is a good predictor of outcome of rehabilitation. Apathy has to be evaluated and systematically assessed during initial admission and while the patients are undergoing a rehab programme.

Rehabilitation of CVA has significant bearing on patients been actively engaged in rehab programme. Apathy, however, hinders such imperative process and may worsen patient's dependency. This in turn prolonged the acquired impairments and limit the rehab.

Research is needed in areas of apathy measurement and appropriate clinical management. Any treatments will have significant impact on patients' quality of life and progress, as well as reducing the burden of caregivers. Economic benefit in reduction in cost is also indicated as apathy is reduced.

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