

Introduction

Frontal-subcortical syndrome (FSCS) is a broad-range of clinical syndromes. The main such predictors; therefore, we feel that understanding each of this syndrome's components' relation with FSCS is fundamental to build a solid approach to this disease.

Insulin resistance and FSCS

Insulin resistance is a bodily state in which higher levels of insulin are necessary to produce the same biological response that normal levels used to do [12]; it comprises both pre-diabetes and diabetes mellitus type 2.

endothelial damage [14], other groups have shown a role for advanced glycation end-products (AGEs) and eicosanoids [15-17]. It has been also demonstrated that diabetic patients can have superior cognitive function, including executive function, deficits [18,19], and elaborate neuroimaging studies in patients with this profile demonstrated that the deficit may be due to microvessel and axonal damage in the white matter connections between cortical and subcortical structures, as well as some cortical gray-matter areas [20,21]. Pugh and Lipsitz [2] have called, even before diffusion imaging had been made, this type of microvascular lesion against the white matter as "subcortical ischemic microangiopathy", and shown that it is a major component in the FSCS; Zunker et al. [22] had previously shown, in a clinical study, that patients with cerebral microangiopathy have higher insulin plasma levels than control patients. Taking together this body of evidence, it is reasonable to state that insulin resistance is a main risk factor for FSCS.

Obesity and FSCS

Obesity, commonly defined as a body mass index (BMI) equal or higher than 30, is an established cardiovascular risk factor; what is becoming increasingly discussed is its role as a risk factor for

the development of insulin resistant through the same inflammatory pathways [24,26], which *per se* is a major risk factor for FSCS (see section 3.1).

Dyslipidemia and FSCS

There is controversial evidence that dyslipidemia (high blood LDL, high blood triglycerides, or low blood HDL) is linked to FSCS. Grottemeyer et al. have successfully demonstrated that, in humans, ischemic brain disease – comprising stroke, transient ischemic attack, and small-vessel disease – is associated with elevated plasma viscosity, which in turn is proportional to, amongst other factors, the concentration of plasma lipids [29]; however, leukoaraiosis, a surrogate measure of cerebral white matter small-vessel disease, is inversely associated with plasma lipid levels, which could indicate a protective role of these molecules against small-vessel disease [30]. In the study conducted by Roriz-Cruz et al. in 2007 on elderly people with metabolic syndrome and FSCS [3], total blood cholesterol was one of the few metabolic syndrome components that did not show a statistically significant association with the presence of FSCS, even though triglyceride levels did – this may suggest that the relationship between dyslipidemia and FSCS is more complex than it seems at first sight, and so that more studies must be made before we can draw any definitive conclusion about it.

Hypertension and FSCS

The relationship between hypertension and FSCS is thought to be due to the role of high blood pressure in promoting small-vessel disease: according to a recent review by Østergaard et al. [31], hypertension causes small-vessel disease by leading to pericyte degeneration, swelling of endothelium and surrounding astrocytic vascular feet, and thickening of the basement membrane; enlarged perivascular space has also been reported as a consequence of hypertension [32]. Although there is plenty of evidence that hypertension is a major risk factor for small-vessel disease [33], there is also a striking paucity of data from the medical literature on whether anti-hypertensive treatment provides any benefit for this condition.

Frontal Release Reflexes and FSCS

Frontal release reflexes (FRRs), sometimes also called “primitive reflexes”, are a central part of FSCS: while small-vessel disease probably accounts for the major pathophysiologic component of the syndrome, FRRs form the cornerstone of its diagnosis: For a patient to be considered as having FSCS, a commonly adopted diagnostic criterion is the presence of at least one FRR plus three or more of the following: cognitive impairment; late-onset depression; lower-limbs neuromotor dysfunction; and urgency urinary incontinence [3]. FRRs consist in early-life reflexes that are normally suppressed along the maturation of the frontal lobe and its connections, being thus absent in a normal individual after its infancy [34]. Since the disappearance of these reflexes relies on frontal lobe activity, damage to this brain area or its connections may result in the reappearance of one or more of these signs, as shown by studies evaluating the features of bilateral anterior cerebral artery infarction [35] and subcortical infarction of frontal-subcortical pathways [36]. Age-induced hypometabolism of frontal cortex or putamen – structures involved in the corticostriatal motor circuit (see section 2) – as assessed by PET scanning was also associated with the presence of FRRs [37] confirms that such circuit function is necessary to suppress the primitive reflexes; as the pathophysiology of FSCS is determined by damage to these and other fibers, it makes sense that the syndrome should compromise the inhibition of primitive reflexes, leading to their release.

The palmonental reflex, which consists in an involuntary contraction of chin and eyelids in response to painful thenar stimulations, is a high-specific and low-sensitive test to detect for frontal lobe anatomical lesions [38]; however, still a significant share of health adult population can present this sign incidentally, and so usually more than just one positive FRR is necessary to indicate frontal damage without other signs [39]. There is currently not conclusive accuracy data for the other FRRs, but one can wonder that their sensitivity and specificity may behave as the ones of the palmonental reflex, since they are caused by the same kind of damage. Other common FRRs are the grasp reflex (hand and fingers contraction in response to palmar pressure stimulus), the sucking reflex (sucking movements with the lips when an object such as a spatula is inserted) (TW 9 9 313.2283 592p)-5(a)ID 240 BDC BT/

Citation: Starosta RT, Vidor MV, Roriz-Cruz M (2016) The Frontal-subcortical Syndrome. J Alzheimers Dis Parkinsonism 6: 247. doi: [10.4172/2161-0460.1000247](https://doi.org/10.4172/2161-0460.1000247)

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