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Introduction

Frontal-subcortical syndrome (FSCS) is a broad-rang4.1(b8b8b TETEMC /Span <</MCID 27 >>BDC BT/T11 1 Tf0 Tw 9 0 0 9 42.5197 494.7378 Tm([

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 cardiovascular disease

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. AlrshTf0.ec9(et)T(hi)uxabeT(h10 1 s)4(u)rdiu tone siet

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, de cits [18,19], and elaborate neuroimaging studies in patients with this pro le demonstrated that the de cit 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 di usion 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 de ned 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 in ammatory pathways [24,26], which *per se* is a major risk factor for FSCS (see section 3.1).

D i ide ia a d FSCS

ere is controversial evidence that dyslipidemia (high blood LDL, high blood triglycerides, or low blood HDL) is linked to FSCS. Grotemeyer 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 signi cant 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 rst sight, and so that more studies must be made before we can draw any de nitive conclusion about it.

H e e i a d FSCS

e 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 bene t for this condition.

F a Re ea e Re e a d FSCS

Frontal release re exes (FRRs), sometimes also called “primitive re exes”, 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 re exes that are normally suppressed along the maturation of the frontal lobe and its connections, being thus absent in a normal individual a er its infancy [34]. Since the disappearance of these re exes 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] con rms that such circuit function is necessary to suppress the primitive re exes; as the pathophysiology of FSCS is determined by damage to these and other bers, it makes sense that the syndrome should compromise the inhibition of primitive re exes, leading to their release.

e palmomental re ex, which consists in an involuntary contraction of chin and eyelids in response to painful thenar stimulations, is a high-speci c and low-sensitive test to detect for frontal lobe anatomical lesions [38]; however, still a signi cant 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]. ere is currently not conclusive accuracy data for the other FRRs, but one can wonder that their sensitivity and speci city may behave as the ones of the palmomental re ex, since they are caused by the same kind of damage. Other common FRRs are the grasp re ex (hand and ngers contraction in response to palmar pressure stimulus), the sucking re ex (sucking movements with the lips when an object such as a spatula is inseT/T(r)13(Tw 9 9 313.2283 592p)-5(a)ID 240 BDC BT/

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