ABNORMALLY INCREASED IRON CONCENTRATION IN BASAL GANGLIA IN SHY-DRAGER SYNDROME

MR IMAGING AND AUTONOMIC STUDY

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SUMMARY — Report of an early case of Shy-Drager syndrome in a 67 year-old woman patient. Autonomic failure was diagnosed by functional evaluation as well as laboratory tests. MR imaging disclosed a prominent putamina hypodensity in T_2-weighted images at high field strength due to iron increased depositing in this basal ganglia. MR imaging evidences confirm Shy-Drager syndrome diagnosis, and contributes for differential diagnosis of idiopathic hypotension (pure autonomic failure) in special in SDS early cases.

Concentração de ferro anormalmente aumentada nos núcleos da base na síndrome de Shy-Drager: RM imagem e estudo autonômico.

RESUMO — É relatado o caso de unm paciente de 67 anos de idade com quadro inicial da síndrome de Shy-Drager. O diagnóstico foi possível por provas funcionais autonômicas e exames laboratoriais. A ressonância magnética cerebral (contraste baseado na densidade de prótons e em T_2) objetivou proeminente hipodensidade putaminal em T_2, secundária ao aumento do depósito do ferro nesta região. Esse achado da RM confirma o diagnóstico da síndrome de Shy-Drager e permite diferenciá-la da hipotensão ortostática idiopática, particularmente na fase de início da SSD quando os sinais de comprometimento do SNC são discretos ou estão ausentes.

Described in 1960 31, the early clinical features in Shy-Drager syndrome (SDS) are postural symptoms during many years[24]. Central nervous system signs (extrapyramidal, pyramidal or cerebellar) are observed two to five years after orthostatic hypotension diagnosis 34,36. The Shy-Drager patients do not respond well to antiparkinsonian drug therapy, and usually succumb to the disease seven to eigth years after its onset and four to five years after CNS disorders outset 35. Postmortem SDS findings include gliosis and/or neuronal loss in the substantia nigra, caudate nucleus, putamen, cerebellar cortex, pontine nuclei, and inferior olives 28. The neuropathologic SDS findings were divided in two groups 24, the first group is characterized by a striatonigral degeneration with Lewy corps 15,29; the second group by a striatonigral degeneration or olivopontocerebellar atrophy without Lewy corps 31 (two cases in the original Shy-Drager publication). The dominant neurochemical finding in autopsy studies is a severe dopamine decrease in the striatum, substantia nigra, and nucleus accumbens[4]. In vivo studies by evidence of serotonin decrease (autonomic failure) and dopamine decrease (extrapyramidal signs) metabolism in CSF is established by probenecide test[24]. The autonomic evaluation findings in SDS include a sympathetic

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and parasympathetic disorder 24 due to degenerative neuron loss in the intermediolateral column of spinal cord responsible for central disorder of cardiovascular reflex.

Classically SDS was distinguished from Parkinson autonomic failure 12 and idiopathic orthostatic hypotension[4] by chronological clinical features, autonomic evaluation and follow-up of the potients2. More recently 6,10,26,30 high tield MR imaging used for analysing the iron distribution in the brain establishes abnormally increased iron concentration (decreased T_2 relaxation times) in the putamen and lateral pars compacta of the substantia nigra in Shy-Drager patients. These MR imaging evidences confirm SDS diagnosis and may also potentially serve to differentiate this syndrome from idiopathic orthostatic hypotension (pure autonomic failure) in special in the early course of the disease when other clinical manifestations may be minimal or lacking 6.

CASE REPORT

SCM, a 67 year-old white married woman born in Sao Oarlos (State of Sao Paulo) was admitted to Clinical Hospital, Faculty of Medical Sciences, State University of Campinas in March, 21, 1990 with a history of postural symptoms with syncope, heat intolerance with anhydrosis, developed two years ago. She was unable to stand up because a dizziness sensation or syncope without paleness, nausea or vomiting. Syncope was not associated with sphincteric or motor manifestations or mental confusion. Her past medical records were unremarkable. She has no family history of neurologic or autonomic diseases. At admission her physical examination objectives an orthostatic hypotension without pulse rate changing (asympathicotonic type 37) (Fig. 1). She had a syncope without pallor after two minutes standing up. Prompt relief was achieved when she returned to supine position. She was classified severe grading following criteria of autonomic failure according to Cohen et al. 9. The remaining of her physical examination was normal. Neurological examination yielded a hyperactive patellar deep tendon reflex, and slight amyotrophy of small muscles of the hands. The autonomic evaluation comprised a Valsalva maneuver, cold pressor test, atropine injection, and plasma levels of adrenaline, noradrenaline, dopamine, renin activity and aldosterone. The HR response in Valsalva maneuver characterised a double branch disorder, sympathetic and parasympathetic, of cardiovascular reflex arc (no tachycardia in phase II, and no bradychardia in phase IV) (Fig. 2). The cold pressor test, and atropine injection test

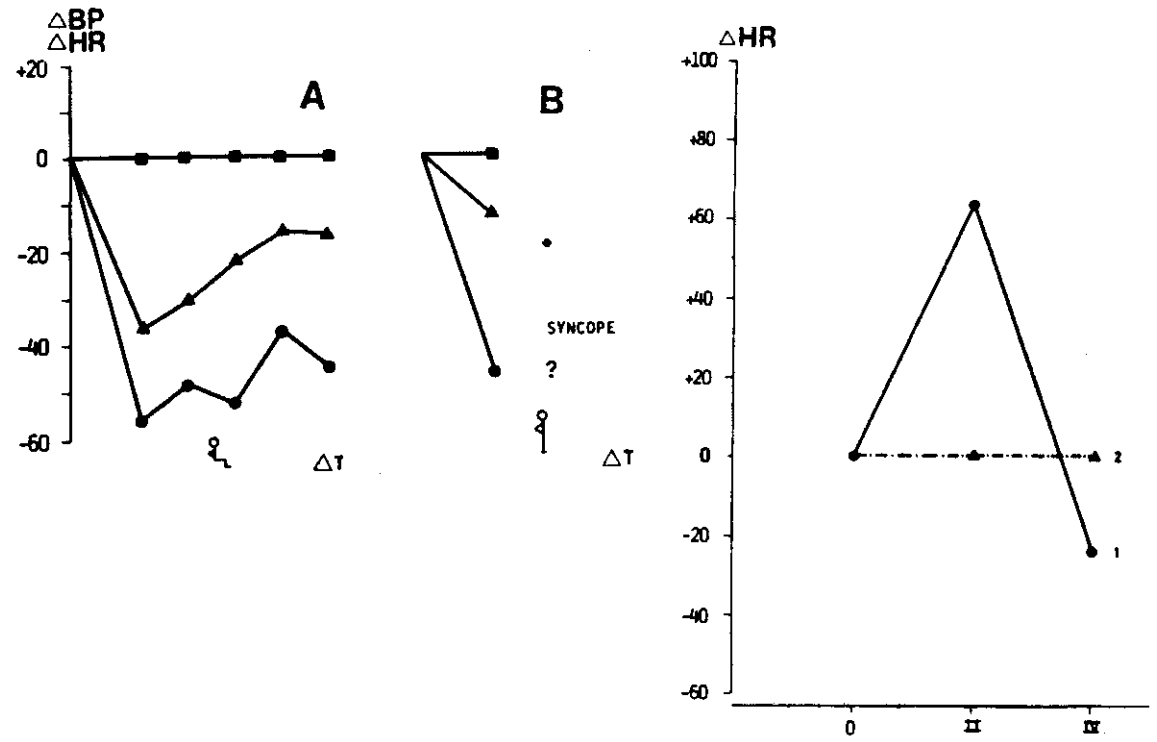

Fig. 1 (left) — Postural changing in heart rate (□), systolic blood pressure (●) and diastolic blood pressure (△) in seated position (A) and upright position (B) in Shy-Drager patient. Syncope was observed after two minutes upright (✱).

Fig. 2 (right) — Maximal heart rate changing during phase II and phase IV of Valsalva maneuver in Shy-Drager patient (2) in contrast to normal subjects (1).

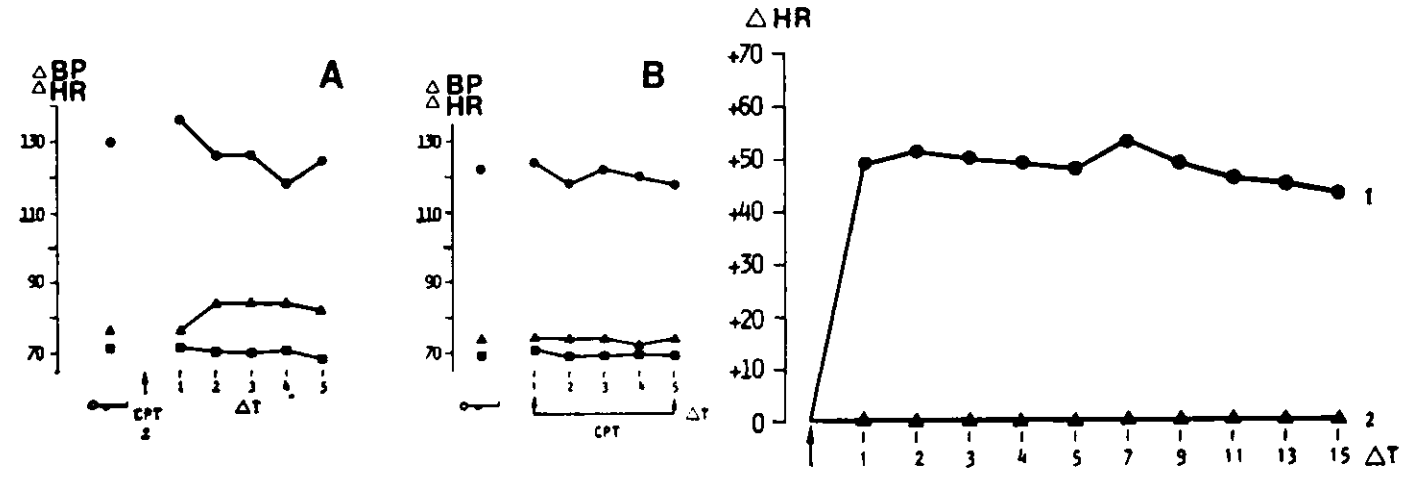

Fig. 3 (left) — Heart rate (□), systolic blood pressure (●) and diastolic blood pressure (Δ) after one minute of hand immersion (A) and during five minutes hand immersion (B) of cold-pressure test (CPT) in Shy-Drager patient.

Fig. 4 (right) — Heart rate changing after 3mg intravenous atropine injection (arrow) in Shy--Drager (2) in contrast to normal controls after 1.25mg (1).

(1.5 mg and 3 mg intravenous) corroborated the sympathetic branch disorder of cardiovascular reflex (Figs. 3 and 4). The serum aldosterone was normal. The plasmatic renin activity was decreased in supine position (0.29^g/ml/h, normal range 1.2+1.1) and increased in orthostatism (0.48^g/ml/h, normal range 2.6+1.3). Plasma noradrenaline was slightly low at rest (86pg/ml, normal range 100-350) little increasing after two minutes of standing up (92 pg/ml) and falling after five minutes of orthostatism (77 pg/ml). Plasma adrenaline was normal in supine position (21 pg/ml, normal range 20-50), slowly increasing after two minutes of standing up (26 pg/ml) and falling after five minutes in orthostatic position (15 pg/ml). Plasma dopamine was normal at rest (34 pg/ml, normal range 20-50), increasing after two minutes in orthostatism (49 pg/ml) and falling after five minutes of standing up (27 pg/ml). The routine laboratory tests were normal. MR imaging disclosed a putaminal hypointensity in T^-weighted images at high field strenght (Fig. 5). The decrease signal intensity of putameh is more prominent than that of the globus pallidus, and it is due to iron increasing distribution in this place.

COMMENTS

Piorry27 i„ 1826 is the first to describe an orthostatic syncope. Babinski and Laubryl in 1924 are the first to trace the outline of postural hypotension, and Bradbury and Eggleston 4 in 1925 described an orthostatic hypotension with failure of increasing the heart rate in three cases. The incomplete autopsy of one of their cases in 1927 is normal, and Bradbury and Eggleston proposed a hypothesis of a peripheral sympathetic abnormality to explain the postural hypotension In 1960 Shy and Drager 31 described a clinical-pathologic study of three cases of orthostatic hypotension associated to diffuse lesions in the CNS. This disorder is due to a central type lesion of autonomic system 14,21,24 with sympathetic branch and vagal branch disorders in autonomic functional evaluation 24. SDS is a primary preganglionic disorder 9.31. It is suggested by relatively normal resting noradreline in contrast to the marked reduction in other autonomic disorders (acute panautonomic neuropathy 22, diabetic autonomic neuropathy 8). The poor upright response in SDS[37] indicates a failure to activate central sympathetic pathways 8,9,22,40. These findings are consonant with published reports of a marked reduction in preganglionic sympathetic neurons 3,19,22,23,31, including morphometric studies 3,19,22. The heart rate response in phase II and phase IV of Valsalva maneuver demonstrates a sympathetic and parasympathetic failure in SDS 2,24. The poor response to cold pressor test is due to ailment of vasomotor sympathetic efferent pathway 24. The atropine (1.5 to 3.0 mg IV) injection test indicates a disorder of cardiac efferent pathway of sympathetic nerves 17,18,24,25,38,39. This is corroborated by an absence of upright tachycardia when blood pressure falls 24.

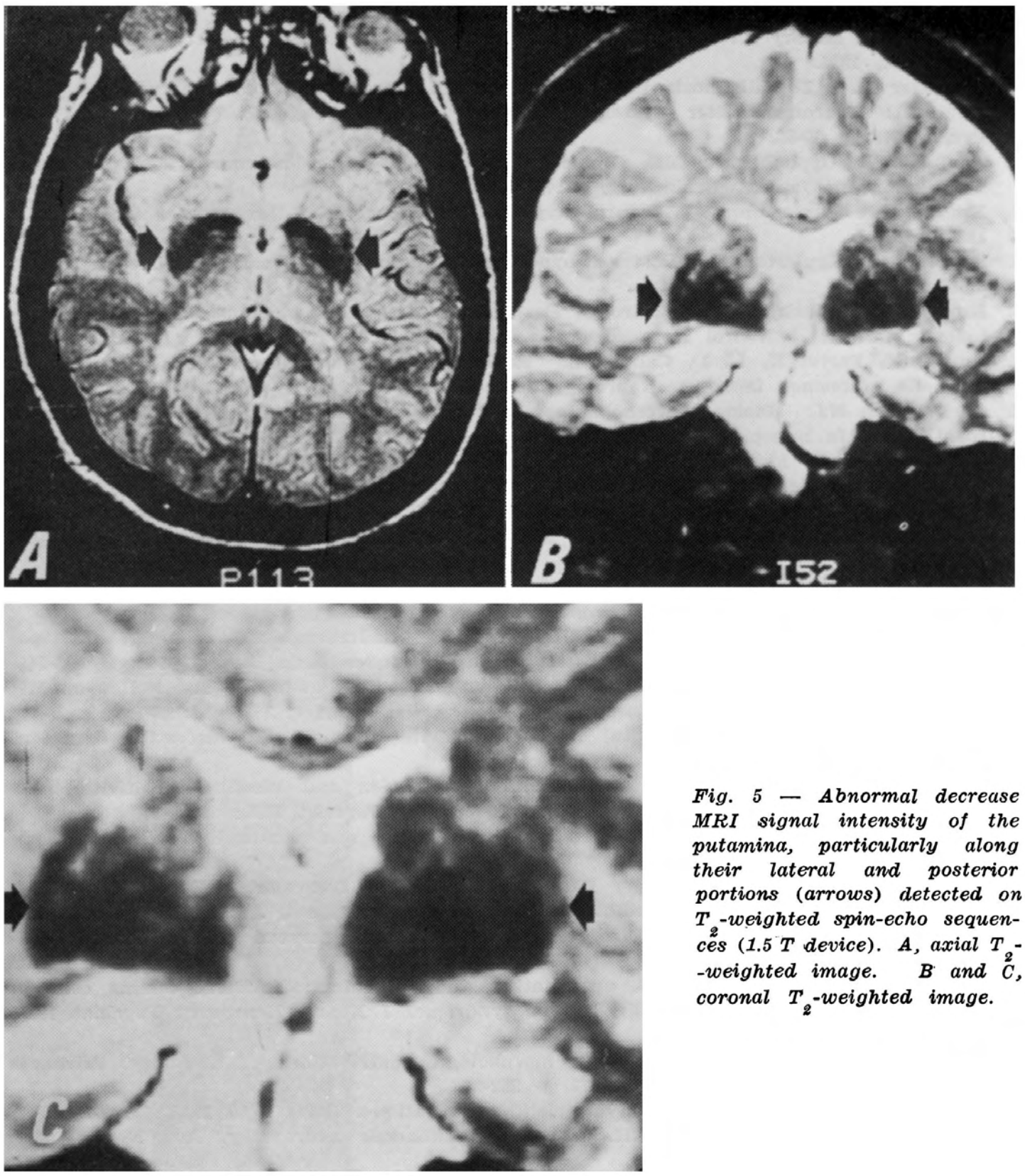

Fig. 5 — Abnormal decrease MRI signal intensity of the putamina, particularly along their lateral and posterior portions (arrows) detected on T_2-weighted spin-echo sequences (1.5 T device). A, axial T_2-weighted image. B and C, coronal T_2-weighted image.

The increased iron concentration evidenciated by MR imaging in putamen and in pars compacta of substantia nigra 6,10,26,30 confirms SDS and distinguishes from idiopathic orthostatic hypotension (progressive autonomic failure) particularly in early cases[6]. There are consonant findings on brain iron concentration between MR imaging !0 and autopsy studies 16. "»

Increased deposition of iron in CNS has been reported in degenerative disorders which affect the basal ganglia (Hallervorden Spatz disease 1[3'33], Huntington disease 20, Parkinson disease u and dystonia[7]). The anatomical region of iron deposition changes in function of etiology of the degenerative disorder. In SDS the local brain iron deposition is particularly suggestive to the disease 6, in special if it is associated to autonomic clinical symptoms and/or CNS signs.

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