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THE AUTOREGULATION OF CEREBRAL BLOOD FLOW, THE CEREBROVASCULAR REACTIVITY AND THEIR INTERACTION IN THE SHY-DRAGER SYNDROME

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ABSTRACT.

The experimental study of the autoregulation of cerebral blood flow, of the cerebrovascular reactivity and of their interaction is performed in a confirmed case of Shy-Drager Syndrome, by means of the xenon-clearance technique.

The basal mean rCBF is slightly depressed.
The cerebrovascular reactivity to variation in P_aCO_2 and to local cerebral activation are maintained.

The inferior threshold of breaking of autoregulation is raised. A competition between the effects on CBF of autoregulation loss and of metabolic regulation is demonstrated. The latency of operation of the autoregulation is evoked by the analysis of the CBF measurements and is confirmed by the simultaneous EEG study.

INTRODUCTION.

The autoregulation of the cerebral circulation was demonstrated as soon as 1939 (Fog, 1939) and its modalities were thoroughly studied on a regional basis by the measurement of the regional cerebral blood flow (rCBF) in normal humans (Lassen, 1959). The mechanism of the cerebrosvascular autoregulation still remains a subject of controversy : arguments in favour of a prominent action of myogenic factors, of neurogenic mechanisms or of metabolic mediators have been controversely put forward (see Olesen, 1974).

The Shy and Drager syndrome provides a model for the experimental study of the cerebrosvascular regulation in man. The published observations (table I) report varying effets of that disease on rCBF regulation. These divergent results could be imputed in part to various degrees of severity of the autonomic nervous damage and, in part, to methodologic discrepancies that will be discussed hereafter with further experimental data.

MATERIAL AND METHOD.

The patient is a 75 years old woman, with a 5-year history of progressively aggravating idiopathic orthostatic hypotension, combined with urinary incontinence, extrapyramidal symptoms and cerebello-vestibular signs (Shy and Drager syndrome).

The absence of any cardiovascular response to the Valsalva manoeuver demonstrated that autonomic arc reflexes were defective. The clinical and physiopathological investigation, according to Johnson and Spalding (1974), suggested a preganglionic site of the lesion. The biochemical study showed an absence of elevation of plasma-noradrenalin level in orthostatism.

The pathological control showed a diffuse degenerative loss of neurones in multiples sites, in particular the strieto-nigral and the olivo-ponto-cerebellar regions and the medullar grey substance, including the intermedio-lateral columns.

The rCBF is measured by the ^{133}Xe clearance technique: the left internal carotid artery is catheterized from the common carotid, after a local anaesthesia without any vasoconstrictive substance ; five mCi of ^{133}Xe in 1 ml of saline are manually injected ; the radioactivity of the left cerebral hemisphere is detected by a Nuclear Enterprises gammacamera and is recorded by successive 2 second blocks on a 4096-channels Tridac Multi-8 Intertechnique System.

The 2 min.-initial slope indexes of 30 regions are computed off-line through a least-square adjustment of the curves. The half-confidence interval of the monoexponential slope estimation is computed at $p < 0.1$ and is expressed, as the brain flow, in ml/min. 100 gr. The p_aCO_2 and the heart level corrected mean arterial blood pressure (MABP) are measured in the internal carotid artery (Hewlett-Packard pressure monitor). Successive measurements are performed with the patient confortably lying on a tilt-table, in a quiet environment, with shaded lights. Any significant saturation of the gammacamera, is avoided by sparing a 20 min. period of xenon elimination between successive measurements, with the patient in horizontal decubitus. Each determination of rCBF is made after 5 min. of steady MABP.

RESULTS.

Basal rCBF

The mean cerebral blood flow in the left hemisphere is 48.2 ± 3.1 ml/min. 100 gr at rest in the horizontal position (MABP = 140 mm Hg, p_aCO_2 = 38 mm Hg), with a slight physiological frontal hyperemia (fig. 1, left). This value is slightly lower than that of normal subjects, as observed by others in cases of Shy-Drager Syndrome (table I).

Hypocapnia

Hyperventilation lowers the p_aCO_2 to 28 mm Hg, without alteration in MABP in horizontal decubitus and induces a mean rCBF value of 41.2 ± 2.9 ml/min. 100 gr without modification in the pattern of rCBF distribution. The sensitivity of the rCBF to variations in p_aCO_2 is of the same order of magnitude than in normal subjects (Reivich, 1964) and in three other cases of Shy-Drager Syndrome (Caronne and Plum, 1972 ; Meyer et al., 1973).

Functional activation by psychomotor activity

Active flexion and extension movements of the right wrist and forearm, performed at injunction, in the horizontal position and in normocapnia are accompanied by a significant hyperemia at the left frontorolandic and frontotemporal cerebral convexities (fig. 1, right).

Drug-induced hypertension

The I.V. infusion of phenylphrin (Neosynephrine Wintrop), at a rate of 0.1 mg/min., induces a rapid rise of MABP up to 200 mm Hg, with tachycardia. The mean rCBF, measured after 3 min. of stable arterial pressure, rises to 51.4 ± 3.7 ml/min. 100 gr. without alteration in its distribution. The rise in rCBF is not significant.

Orthostatic hypotension

The rCBF is measured at different levels of MABP, as obtained at different degrees of passive tilting-up of the patient : the curve of mean rCBF versus arterial pressure (fig.2) reveals a partial loss of autoregulation, with a point of breaking lying between 120 and 100 mm Hg of MABP.

Functional activation by anxiety

The presyncopal state at MABP = 57 mm Hg is accompanied by a paradoxal stabilisation of the mean rCBF (fig. 2) ; the distribution pattern at this level of MABP (fig. 3) shows a deep fall of the rCBF in the posterior regions of the cerebral hemisphere, in the line of the loss of autoregulation but it reveals also a significant hyperemia in the prefrontal area.

DISCUSSION AND CONCLUSION

The Shy and Drager syndrome (Shy and Drager, 1960) is an unique combination of progressive autonomic nervous system failure with other degenerative central nervous system disorders, such as striatonigral and olivo-ponto-cerebellar atrophy (Bannister and Oppenheimer, 1972). Orthostatic hypotension is believed to be the result of lesion of the efferent sympathetic pathway, with a neuronal degeneration in the intermediolateral columns of the spinal cord and a consequent failure in the noradrenaline release (Bannister and al., 1977). The clinical, physio-patho-

logical and neuropathological investigation of the present patient permit to conclude to a Shy - Drager Syndrome. The utmost interest of this pathology is to permit the study of the cerebral circulatory effects of a non pharmacologically induced arterial hypotension in man, and to evaluate the consequences of a totally or partially impaired sympathetical nervous control on the regulatory processes of the brain perfusion.

The regional enhancement of rCBF during the functional activation of the fronto-rolandic neurons (Olesen, 1971) is preserved in this patient (fig. 1, right). This undamaged functional regulation in the presence of total or partial alteration of the autonomic cerebro-vascular innervation is an argument against its neurogenic origin. Furthermore, the frontal hyperemia that is demonstrated in deep arterial hypotension is presumably linked to a functional activation by anxiety and to the fact that the autoregulation process has not exhausted all the capacity of decrease of the cerebral haemodynamic resistances and leaves place for the operation of local metabolic regulation.

The demonstration of a partially broken autoregulation (fig. 2) is not an unequivocal argument for the neurogenic hypothesis : two other etiologies may be invoked : either a rise of the threshold of autoregulation due to the mild basal hypertension, either a result of the repetition of orthostatic ischemic episodes. The partially maintained autoregulation in this case is in accordance with the observation of Skinhoj and al. (1971), and with the intact autoregulation in animals with chronic denervation of the cervical sympathetic chain (Rapela and al., 1967 ; Waltz and al., 1971 ; Ekloff and al., 1971). The different results published by others in similar cases (Table I) may be due to methodological discrepancies rather than to physiopathological discordances : the methods of monitoring of CBF using the arteriovenous difference in oxygen blood content detect very rapid variations in the global CBF, as a result of abrupt orthostatic arterial hypotension and they do not explore sensu stricto the autoregulation process, that was shown to work after several second of latency (Yoshida and al., 1966 ; Boysen and al., 1971 ; Symon and al., 1972) and to be effective after a delay of several tens of seconds to some minutes (Hirsch and Korner, 1964 ; Rapela and Green, 1964 ; Yoshida and al., 1966 ; Ekstrom-Jodal and al., 1970).

A further original experimental argument support in the present case the hypothesis of a <u>delay for the full function of autoregulation</u> (fig. 4) : when the patient is tilted up, her systolic arterial pressure falls fro[illegible] mm Hg to [illegible] mm Hg and stabilizes at this level, without tachycardia ; the patient is initially lipothymic, with a marked global of the EEG but, after 4 minutes, the level of consciousness and the EEG improve, in spite of the persistant deep arterial hypot[illegible]sion. This secondary improvement of the EEG during orthostatic deep hypotension brings an additional evidence for a latency of several minutes for the full operation of the autoregulation process.

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LEGENDS

Figure 1 :

The rCBF of the left cerebral hemisphere in the horizontal position, at rest (left) and during active flexion-extension movements of the right wrist and forearm (right).

Figure 2 :

The mean left hemispheric rCBF, related to the MABP shows a partial loss of autoregulation.

Figure 3 :

The distribution of the left hemisphere rCBF during two episodes of tilt-up hypotension : at right the patient is anxious and shows a marked frontal hyperemia.

Figure 4 :

The EEG and ECG tracings in the recumbent position (systolic arterial pressure = 170 mm Hg) and during a lasting orthostatic hypotension (systolic arterial pressure = 45 mm Hg). The EEG improves after 4 minutes of hypotension.

Table I :

Synopsis of the observations on the CBF in cases of Shy-Drager Syndrome.

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