Similar Autonomic Nervous System Disorders Underlying Cystic Fibrosis and Pancreatic Cysts Allowed Common Neuropharmacological Therapy: Report of Four Cases

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ABSTRACT

We discuss two cases of patients affected by pancreatic cysts and two patients affected by cystic fibrosis showing similar neuroautonomic profile, high adrenal sympathetic activity plus low neural sympathetic activity, who were significantly improved with neuropharmacological manipulations addressed to reverse this profile. Clinical, radiological, and neurochemical assessment showed progressive and sustained improvement throughout more than two years for the cystic fibrosis cases and lasted more than four years for the pancreatic cyst cases in the follow up of both trials. The neuropharmacological therapy addressed to enhance central noradrenergic activity was carried out by the administration of doxepin (noradrenaline uptake inhibitor). Our findings are consistent with the postulation that both syndromes share a common pathophysiological disorder, acinar secretory overflow, which overwhelms the pancreatic duct drainage. Although we have assessed and treated several patients with these pathologies, we refer only to these four well investigated, treated, and followed-up patients.

INTRODUCTION

Our neurochemistry laboratory investigated some 25,000 normal and diseased subjects. Circulating neurotransmitters noradrenaline (NA), adrenaline (Ad), dopamine (DA), plasma free serotonin

(f-5HT), platelet serotonin (p-5HT), tryptophan (TRP), and immunological parameters are routinely assessed before and after neuropharmacological manipulations[1,2] and several stress tests, such as the supine resting plus orthostasis plus exercise.[3] The fact that patients affected by cystic fibrosis and pancreatic cysts presented with several common neuroautonomic disorders led us to go far and in-depth search for common neuropharmacological therapeutic approaches. Although we have assessed many such patients, we will refer only to these four well investigated, treated, and followed patients (two with cystic fibrosis and two with pancreatic cysts).

CASE REPORTS

Case 1

F.D. is a six-year-old girl who was diagnosed as having cystic fibrosis. Her genotype was delta-F 508/delta-F 508. She received pancreatic enzymes to control her diarrhea. She came to our Institute on January 10, 2003. We investigated her exocrine pancreatic function throughout the secretin and starch tolerance tests,[4] confirming absolute pancreatic insufficiency. The autonomic nervous system (ANS) investigation showed absolute adrenal over neural sympathetic predominance (NA/Ad ratio = 1.3; normal ≥ 5). Although platelet serotonin (p-5HT) was elevated (813 ng/mL; 275 ± 20), free serotonin in the plasma (f-5HT) was found to be normal (2.36 ng/mL; normal ≤ 5). Tryptophane (TRP) plasma value was significantly reduced (5,140 ng/mL; normal = 9,000-11,000 ng/mL). In addition, a deficit in respiratory function was revealed by the low FEV_1 value (63% of the predicted value). Immunological investigation showed positive anti-pancreatic (++) and antinuclear antibodies (+). All immunoglobulins were raised. Doxepin, propantheline, and clonidine were administered to this patient and the drug doses were adjusted to her age. Significant clinical, ANS, and immunological improvements were obtained after the first four-week period and continue up to the present (February 2005). The noradrenaline to adrenaline ratio (NA/Ad) and p-5HT returned to normal values; as did plasma TRP value. Anti-pancreatic and antinuclear antibodies were not detected at the fourth four-week period. By December 2004, the patient had grown 5.3 cm and gained 6.9 kg. She continues taking pancreatic enzymes as well as her treatment.

Case 2

M.M.C. is a 5-year-old boy who was diagnosed as having cystic fibrosis in July 2002. At his first visit to our Institute on January 2, 2004, his height was 1.05 m and he weighed 16.6 kg. His genotype was delta-F 508/delta-F 508. He took pancreatic enzymes plus calcium. Lactose tolerance test and starch tolerance were positive (+). ANS investigation showed adrenal over neural sympathetic predominance (NA/Ad = 0.9). Although both p-5HT and f-5HT were significantly raised (824.4 ng/mL and 21.2 ng/mL, respectively), tryptophan plasma values were moderately lowered (7,005 ng/mL). Immunological investigation showed positive (+) anti-pancreatic antibodies and antigliadin IgA and IgG positive (+ in both parameters). This patient received similar treatment to F.D. Significant increases in body weight and height were recorded at each of the 12 following four-week periods. His body weight increased from 16.6 kg to 25.3 kg and his height grew from 1.07 m to 1.15 m. Circulating neurotransmitters assessed at the last visit (February 2005) showed significant reductions of f-5HT (down to 6.2 ng/mL); at the same time, levels of p-5HT decreased steeply (308.4 ng/mL). A significant increase of the previously low NA/Ad ratio was observed, from 0.9 to 5.4 (at orthostasis).

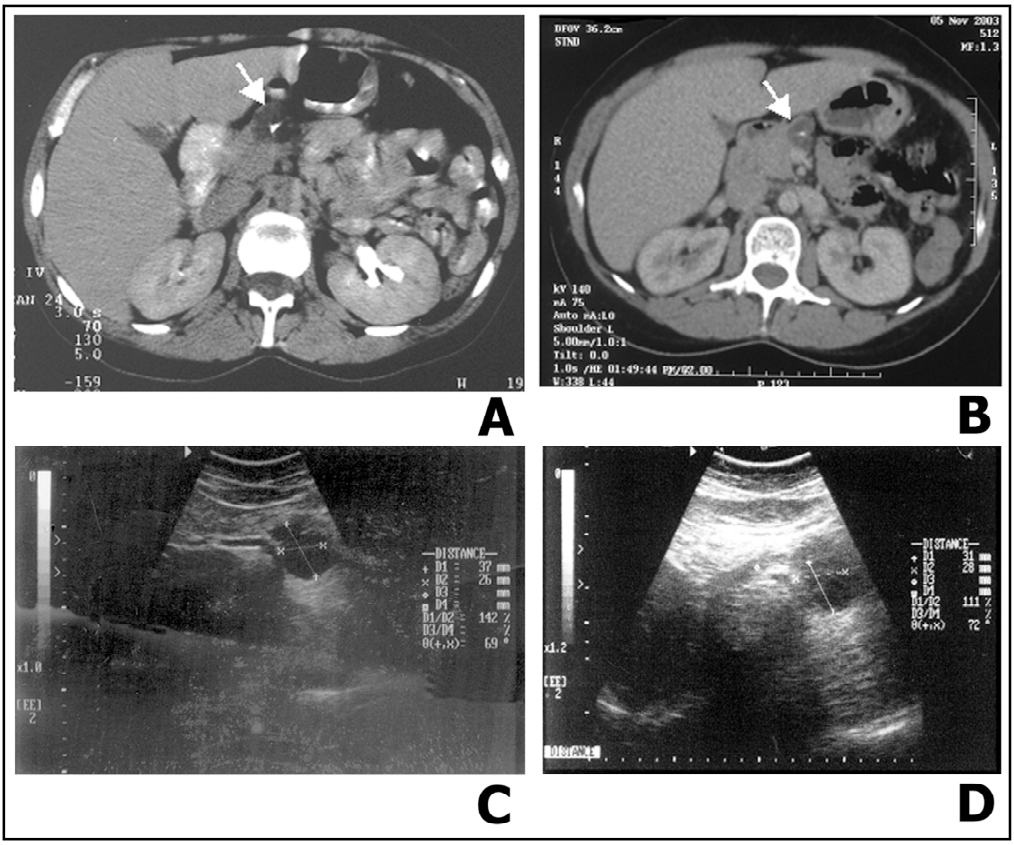

Figure 1. Pancreatic cyst before **(A)** and after **(B)** two years of pharmacological therapy. Significant reduction (60%-70%) was obtained. Pancreatic cyst before **(C)** and after **(D)** seven months of neuropharmacological therapy: Significant reduction (50%-60%) was obtained.

Case 3

A.T.B. is a 44 year-old-woman with three children. She visited us on June 4, 1998, with a pancreatic cyst of 4.5 cm diameter located between the head and the body of the pancreas (Figure 1). It was diagnosed through endoscopic retrograde cholangiopancreatography (ERCP) and laparotomy. Secretin and starch tolerance tests were normal. ANS investigation showed absolute adrenal over neural sympathetic predominance (NA/Ad ratio < 2). Both p-5HT and f-5HT values were greatly increased (923.2 ng/mL and 26.4 ng/mL, respectively). Plasma TRP was found very low (3,420 ng/mL). This patient received the above-mentioned neuropharmacological therapy from June 98 until the present (February 2005), interrupted by frequent two-week holiday breaks. The patient remains asymptomatic and her pancreatic cyst is almost totally reduced (Figure 1). The last p-5HT and f-5HT values were 316.5 and 4.6 ng/mL, respectively.

Case 4

G.R.Y is a 25-year-old woman with two children who visited our institute on July 10, 2001. She presented with a large pancreatic cysts diagnosed by ERCP and echo. The ANS investigation revealed absolute adrenal over neural sympathetic predominance (NA/Ad ratio = 1.5). Both p-5HT and f-5HT showed raised values. Plasma TRP was normal. Neuroautonomic and clinical improvements were obtained through neu-

ropharmacological therapy. The cyst was greatly reduced (50%-60%, Figure 1). The p-5HT value dropped from 963.3 to 345.4, whereas f-5HT fell from 97.4 to 1.5 ng/mL. NA/Ad ratio at orthostasis rose from 0.9 to 5.4.

DISCUSSION

Four patients affected by pancreatic disease, two through cystic fibrosis and two with pancreatic cysts, presented adrenal over neural sympathetic predominance along with raised levels of circulating platelet serotonin (p-5HT). This finding obliges us to consider that these diseases share some common pathophysiological mechanisms. This inference is reinforced by the finding that both clinical and ANS improvements are triggered by similar neuropharmacological manipulation addressed to reverting the Ad over NA predominance. The raised circulating serotonin level found in these two types of pancreatic disease strongly suggests that enterochromaffin-cell overactivity is present in all.[5] Further, the fact that platelet serotonin (p-5HT) was lowered in both types of patients after clinical improvement, suggest that the enterochromaffin cell overactivity was normalized. Both the physiologic disorders and their clinical symptoms are correlated with adrenal over neural sympathetic predominance periods.[6-8] This phenomenon may be associated with the maximal ability of the neural sympathetic system to annul parasympathetic drive which is responsible for enterochromaffin cell secretion.[5] Circulating serotonin arises from enterochromaffin cells that release 5-HT in response to parasympathetic drive.[5] Although most 5-HT is secreted into the intestinal lumen, some fraction reaches portal circulation. Serotonin that escapes to liver and lungs uptakes is trapped by platelets.[7] However, some fraction of serotonin always remains free in the plasma (f-5HT). The normal f-5HT/p-5HT circulating ratio is about 0.5% to 1%. This ratio increases during both platelet aggregation[9] and during any deficit of platelet uptake.[10] Platelet uptake is interfered with by both circulating acetylcholine[10] and circulating DA.[11] The former occurs during excessive parasympathetic drive. The increase of f-5HT registered in these circumstances may be exacerbated because indolamine excites 5-HT_3 and 5-HT_4 receptors located at the medullary area postrema (outside the blood brain barrier), which is connected to the motor vagal complex.[12] This fact results in a further increase of the peripheral parasympathetic drive discharge over the enterochromaffin cells (Bezold-Harisch reflex). In addition, considering the excitatory role played by the parasympathetic system over pancreatic exocrine secretion, it is possible to understand the beneficial effect of neuropharmacological manipulations addressed to bridling the parasympathetic drive through enhancement of neural sympathetic activity. According to the above, it may be postulated that pancreatic cyst formation will be favored by factors that overwhelm the pancreatic duct drainage capacity by excessive acinar cell secretion.

Several ANS and hormonal factors are involved in pancreatic exocrine secretion. Sympathetic nerves terminate on intrapancreatic blood vessels.[13] In addition, inhibition of exocrine secretion may occur in the absence of vascular effects (alpha-receptor blockade), suggesting that the catecholamines may act directly on the secretory cells.[14] Noradrenergic fibers terminate on intrapancreatic ganglia whose stimulation abolishes vagal-induced secretion, by acting at alpha-2 adrenoceptors.[13,14] These findings are supported by the capacity of neural sympathetic enhancement to antagonize the hyper-parasym-

pathetic-induced hypersecretion underlying pancreatic cyst formation.[13-15] Considering that post-ganglionic alpha-2 receptors mediate sympathetic nerves effect, at this level, we find an explanation for the benefits triggered by clonidine (an alpha-2 agonist) in both pancreatic cysts and pancreatitis.[16-18] We also found that a small dose of intramuscular injected clonidine is able to stop abruptly pancreatic secretion from the excretory duct, in experimental dogs.[16] This peripheral NA versus parasympathetic antagonism is consistent with the inhibitory effects exerted by LC-NA axons ending at the dorsal motor nucleus of the vagus located at medullary area.[19,20]

In addition, nicotine receptor antagonists effectively block the vagal-induced pancreatic secretion. This finding fits well with the beneficial effects we obtained by the addition of small doses of propantheline, a nicotine-antagonist that does not cross the blood brain-barrier.

Not only ANS but also hormonal mechanisms are also involved in pancreatic exocrine secretion. The release of both secretin and CCK-pancreozymin are independent of the ANS influence.[18,21-24] However, ANS drives are able to interfere with secretory hormone release and/or its effects.[18] For instance, alpha-adrenergic influences are able to interfere with CCK-pancreozymin effects.[18,21-24] Thus, we believe that the therapeutic success we obtained with this small casuistic has enough scientific support to attempt further neuropharmacological approaches for treatment of these patients.

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