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Prolactin: A Diabetogenic Hormone*

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Summary. During an oral glucose tolerance test (OGTT) glucose and insulin levels were measured in 26 patients with prolactin-producing pituitary tumours without growth hormone excess. Basal glucose and insulin levels did not differ from the values of an age-matched control group. After glucose load the hyperprolactinaemic patients showed a decrease in glucose tolerance and a hyperinsulinaemia. Bromocriptine (CB 154), which suppressed PRL, improved glucose tolerance and decreased insulin towards normal in a second OGTT. – Human PRL or CB 154 had no significant influence on insulin release due to glucose in the perfused rat pancreas. – These findings suggest a diabetogenic effect of PRL. CB 154 might be a useful drug in improving glucose utilization in hormone-active pituitary tumours.

Key words: Prolactin, insulin release, glucose tolerance, pituitary tumours, pancreas perfusions, bromocriptine.

Acute administration of ovine prolactin (PRL) has been shown to influence glucose metabolism in animals [1, 2], to impair glucose tolerance in hypopituitary dwarfs and in hypophysectomized juvenile-type diabetics [3], and to stimulate lipid metabolism [4]. In order to study the long term effects of endogenous PRL on glucose tolerance and glucose-induced insulin secretion, patients with hyperprolactinaemia were investigated. In vitro experiments with the isolated perfused rat pancreas were undertaken to elucidate the direct effect of hPRL on insulin release.

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Material and Methods

a. In vivo-Study

Fifteen female and 11 male patients with hyperprolactinaemia were studied (Tab. 1). Twenty-four patients had a pituitary tumour, one had a craniopharyngioma and one had a normal sella turcica. A galactorrhoea-amenorrhoea syndrome was observed in 9 women. The average body weight was 13 ± 4% above the ideal body weight and the average age was 34 ± 2 years (mean ± SEM). None of the patients had elevated plasma growth hormone concentrations. Eighteen patients had blunted hGH-secretion after insulin-induced hypoglycaemia. In six subjects TSH levels before and after TRH stimulation were below the lower limit of detection; six patients showed TSH values which were subnormal and two suffered from primary hypothyroidism. Thirteen had secondary hypogonadism, eleven had a latent or manifest secondary adrenal insufficiency and three had diabetes insipidus. The mean basal PRL level ($\bar{x}$ ± SEM) measured by radioimmunoassay [5] was 2422 ± 800 ng/ml ranging from 47 to 18 860 ng/ml. Our normal range for men is 8.5 to 25 ng/ml and for women up to 37.5 ng/ml. Fourteen patients were on appropriate hormone replacement therapy at the time of the study. Hypothyroidism was treated in all cases except two (Tab. 1) in order to avoid effects of low thyroid hormone levels on glucose tolerance.

Fifteen patients (nine females and six males) were treated with bromocriptine (CB 154) 3 to 10 mg daily for at least one week and on average for five weeks (upper part of Tab.1).

Plasma prolactin, glucose tolerance and insulin release were determined again under treatment. After an overnight fast oral glucose tolerance tests (100 g) were performed between 8 and 9 a. m. Blood samples were taken just before (0 min) and 30, 60, 120 and

Table 1. Summary of the clinical data of the hyperprolactinaemic patients. 1) Mean basal hPRL levels ± SEM. Number in parenthesis = number of determinations on different occasions. 2) Cortisol: + = basal cortisol (> 4 μg/100 ml) and ACTH-stimulated (25 I. U.) cortisol (> 23 μg/100 ml) and adequate increase of cortisol on insulin-induced hypoglycaemia. (+) = no significant cortisol increase during insulin-induced hypoglycaemia. 3) Luteinizing hormone (LH): + = normal before and after 25 μg LH-RH i. v. (Δ LH > 2,5 ng/ml). 4) Growth hormone (hGH): + = normal basal (< 5 ng/ml) and stimulated levels (> 40% increment above baseline) following insulin-induced hypoglycaemia or arginine i. v. 5) Thyrotropin (TSH): + = normal (Δ TSH > 2.6 μU/ml) before and after 200 μg TRH i. v. (+) = insufficient TSH response after TRH. 6) Diabetes insipidus was diagnosed by serum (> 301 mosm/kg) and urine (< 700 mosm/kg) osmolality after a thirst period up to 18 hours. 7) P. A. = Pituitary adenoma (X-ray) G. A. S. = Galactorrhea-Amenorrhea-Syndrome. For further analytical details (21)

Patient	Sex	Age	% ideal body weight	Basal hPRL ng/ml 1)	Cortisol 2)	LH 3)	hGH 4)	TSH 5)	Diab. insipidus 6)	Diagnosis 7)	Replacement Therapy
A.W.	M	32	+47		+	−	−	+	−	P.A.	−
R.A.	M	52	+ 6		+	+	(+)	−	−	P.A.	T_4
G.M.	M	39	+19		+	−	−	(+)	−	P.A.	testosterone, T_4
A.S.	M	29	+17		−	−	−	+	−	P.A.	cortisol
H.Q.	M	34	+13		−	−	−	−	+	P.A.	cortisol, T_4, ADH, testosterone
H.G.	M	30	+10		−	−	−	−	+	P.A.	cortisol, T_4, Tegretal^R, testosterone
C.H.	F	28	−16		−	−	−	−	−	P.A.+G.A.S.	−
E.F.	F	35	+11		+	(+)	−	+	−	P.A.+G.A.S.	−
J.H.	F	26	−5		+	+	+	+	−	P.A.	−
E.M.	F	25	+7		+	+	+	+	−	P.A.+G.A.S.	−
C.W.	F	19	−3		+	+	−	(+)	−	P.A.+G.A.S.	−
B.P.	F	24	−2	See Table 2	+	+	+	+	−	P.A.+G.A.S.	−
R.M.	F	40	+21		−	−	−	+	+	P.A.+prim. hypothyroidism	cortisol, T_4, Tegretal^R
S.L.	F	24	+10		+	+	+	+	−	P.A.+G.A.S.	−
M.O.	F	38	+19		+	−	−	(+)	−	P.A.	T_4, oestrogens
M.H.	M	33	+11	452± 44 (8)	(+)	−	−	+	−	P.A.	−
A.H.	M	50	+51	4221±161 (9)	+	+	−	+	−	P.A.	T_4
K.W.	M	50	+30	47± 3 (3)	−	−	−	+	−	P.A.+prim. hypothyroidism	cortisol, T_4, testosterone
B.P.	M	22	+4	2524±947 (4)	−	+	−	+	−	P.A.	cortisol
J.R.	M	51	+32	1412± 18 (3)	−	−	−	−	−	P.A.	cortisol, T_3, testosterone
I.S.	F	21	−14	384 (1)	+	+	+	(+)	−	P.A.+G.A.S.	−
R.W.	F	44	−4	140 (1)	+	+	−	+	−	amenorrhea, no tumour	−
A.S.	F	26	−20	113± 10 (6)	+	+	−	(+)	−	P.A.+G.A.S.	−
B.T.	F	32	±0	298± 74 (2)	−	+	+	+	−	P.A.	cortisol
C.K.	F	29	+32	63 (1)	(+)	+	−	(+)	−	craniopharyngioma	cortisol, T_4
R.W.	F	38	+61	3229± 78 (7)	+	(+)	+	−	−	P.A. +G.A.S.	T_4

180 min after glucose loading. Serum insulin was determined by radioimmunoassay [6]. PRL or bromocriptine did not interfere with the insulin assay. Blood glucose was measured by the hexokinase method [7].

The results from the hyperprolactinaemic patients were compared with a control group of ten males and six females, with an average age of 36 ± 3 years (mean ± SEM) and an average body weight of 99 ± 2% of ideal body weight. The data were analyzed for statistical significance using the paired Wilcoxon test.

b. In vitro-Study

For the in vitro experiments, overnight fasted male Sprague-Dawley rats were used as pancreas donors. Pancreatic perfusions were carried out as published earlier [8]. Human PRL was purified by column chromatography [9] from serum of one of our patients with an extreme hyperprolactinaemia (H. Q. in Tables 1 and 2), and was added to the perfusion medium at a concentration of 50 and 250 ng/ml. Bromocriptine was perfused at 20, 100 and 200 μg/100 ml.

Results

a. In vivo-Study

Basal glucose and serum insulin values in hyperprolactinaemic patients and normal subjects did not differ significantly. After a glucose load the patients with prolactin excess showed a markedly reduced glucose tolerance and an enhanced and delayed insulin

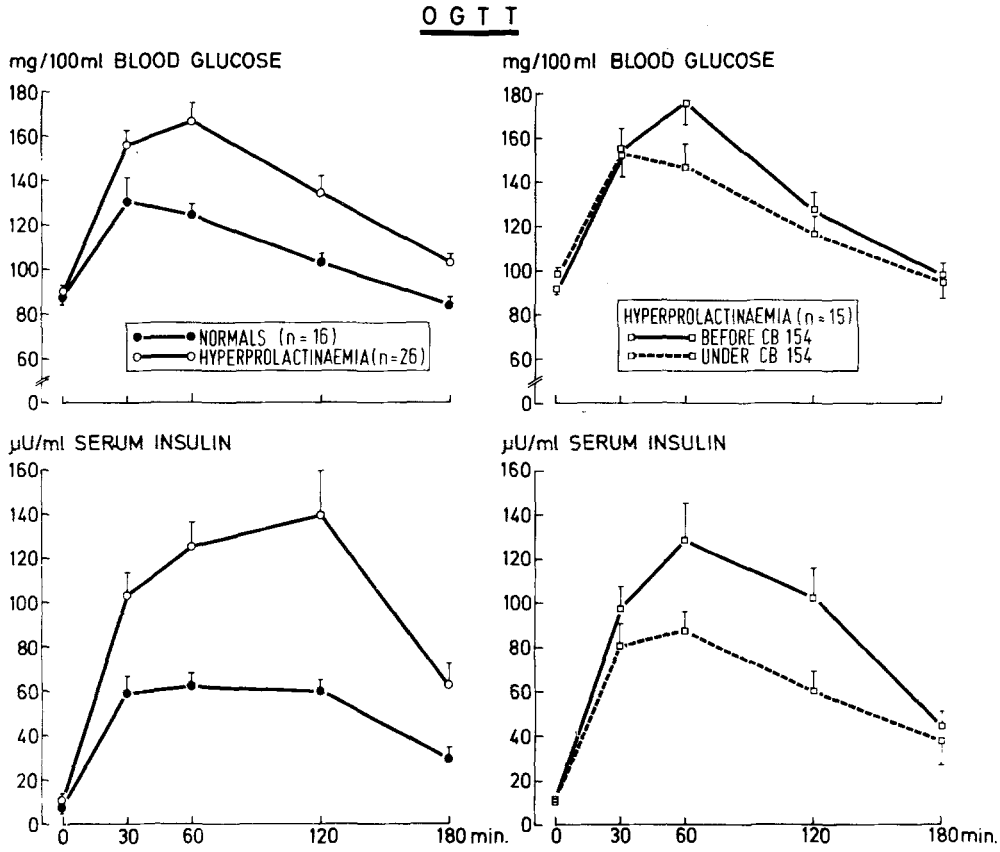

Fig. 1. Left side: Blood glucose and serum insulin values ($\bar{x} \pm$ SEM) in normal subjects and hyperprolactinaemic patients before and after oral glucose loading. Right side: Blood glucose and serum insulin values ($\bar{x} \pm$ SEM) in patients with hyperprolactinaemia before and after CB 154 during an oral glucose tolerance test (OGTT)

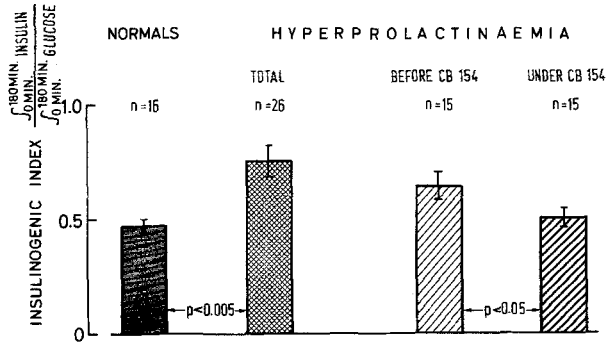

Fig. 2. Insulinogenic indices (mean ± SEM) for normal subjects, all hyperprolactinaemic patients and those patients who were examined before and after CB 154 treatment. The insulinogenic index was calculated using the sum of the increments of insulin and glucose responses to the OGTT

response (Fig. 1, left side). This is in agreement with recent findings from Tourniaire et al. [10]. Fifteen of the hyperprolactinaemic patients were treated with CB 154; as shown in Table 2 the PRL levels were suppressed by 86 ± 3%. At the same time glucose tolerance was improved and glucose-induced insulin release reached almost normal values (Fig. 1, right side).

Calculating the insulinogenic index, a significant increase was observed in the hyperprolactinaemic patients when compared to the control group (Fig. 2). Comparison of the insulinogenic index in patients before and after CB 154 revealed a clear decrease under treatment. The value obtained did not differ from that of the control subjects (Fig. 2).

b. In vitro-Study

To determine whether the PRL and CB 154 effects observed in vivo were mediated through a direct action of these substances on the pancreatic B-cell, in vitro experiments with the isolated perfused rat pancreas were undertaken during glucose stimulation. As shown in Figure 3 the glucose-stimulated insulin release in the perfused pancreas slightly decreased after addition of hPRL (top panel) or CB 154 (bottom panel). However, the suppressive effects of these substances were not statistically significant.

Discussion

The disturbances of glucose tolerance and glucose-induced insulin release observed in the hyperprolactinaemic patients did not correlate with any of the

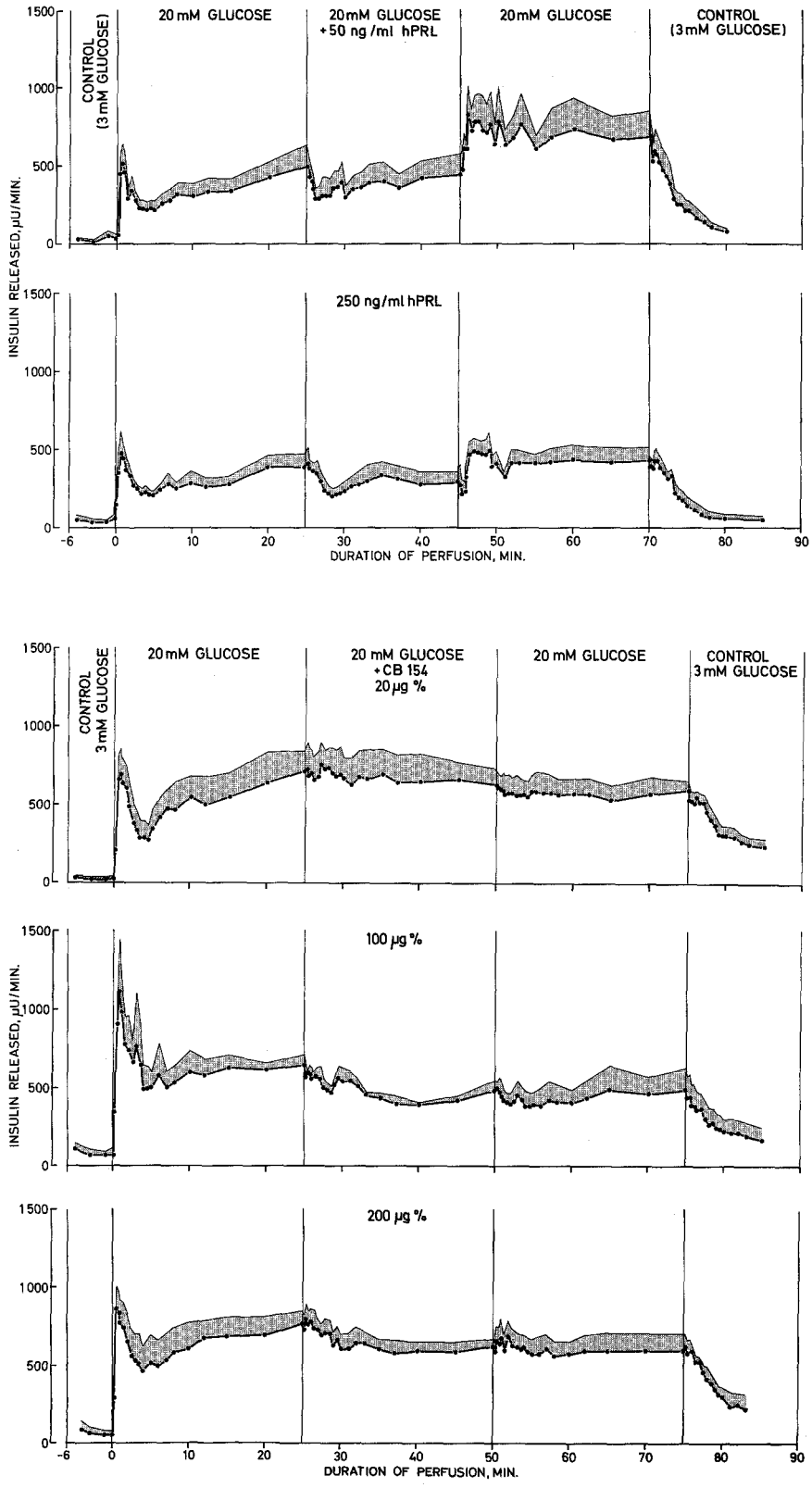

Fig. 3. Insulin secretory profiled induced by sequential perfusion of glucose and glucose plus hPRL (top) or glucose plus CB 154 (bottom) at concentrations indicated in the graphs. Mean values ± SEM for three animals under each condition

Table 2. Basal prolactin levels ($\bar{x} \pm$ SEM) in 15 patients with hyperprolactinaemia before and under CB 154 treatment. Number of determinations on different occasions in parenthesis. For clinical details see Table 1 (upper part)

Patient	hPRL before CB 154 treatment ng/ml	hPRL under CB 154 treatment ng/ml	% suppression of hPRL by CB 154 treatment
W.A.	638 ± 22 (8)	13 ± 2 (8)	98
R.A.	1299 ± 136 (5)	88 (1)	93
G.M.	4411 ± 303 (11)	1146 ± 165 (3)	74
A.S.	5458 ± 532 (10)	236 (1)	96
H.Q.	18860 ± 867 (8)	233 ± 29 (9)	99
H.G.	10218 ± 193 (2)	325 ± 27 (5)	97
C.H.	2717 ± 59 (6)	581 (1)	79
E.F.	119 ± 8 (6)	24 (1)	80
J.H.	2037 ± 25 (4)	176 ± 24 (5)	91
E.M.	125 ± 9 (4)	58 ± 6 (6)	54
C.W.	364 ± 19 (3)	21 ± 5 (3)	94
B.P.	140 ± 4 (8)	11 ± 2 (5)	92
R.M.	2674 (1)	815 (1)	70
S.L.	917 ± 39 (8)	166 ± 7 (4)	82
M.O.	99 (1)	4 (1)	96

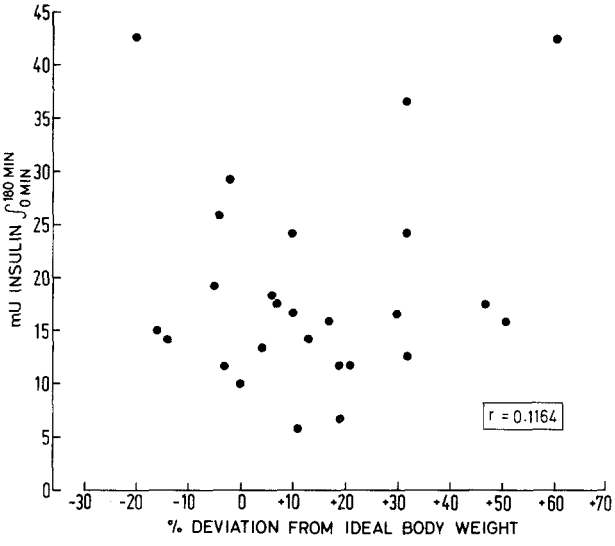

Fig. 4. Relation between the deviation from ideal body weight and the integrated insulin output in the patients with hyperprolactinaemia (n=26). r = correlation coefficient

endocrine deficiencies seen in our patients (Tab. 1). There was also no direct relation between body weight and integrated insulin release in the hyperprolactinaemic patients (Fig. 4). Since the body weight of our patients did not change during CB 154 treatment, the possibility that the improvement of the glucose metabolism and hyperinsulinaemia could be attributed to changes in body weight could be ruled out. No sex difference could be observed.

Although there was no correlation between the absolute PRL levels and the degree of metabolic alterations, we concluded, especially in view of the CB 154 data, that the hyperprolactinaemia was responsible for our findings.

The improvement in glucose tolerance tended to be more marked in those patients who showed a greater suppression of their prolactin levels with bromocriptine.

The lack of correlation between the severity of PRL excess and the degree of glucose imbalance and hyperinsulinaemia might reflect discrepancies between the immunoreactivity of PRL and its biological activity. The existence of circulating immunoreactive hormones with reduced biological activity has been amply demonstrated, especially for hGH [11].

The mechanisms involved in prolactin-induced changes in glucose homoeostasis and insulin release are unknown. In animal studies some results are compatible with the findings in our patients; others are not.

Daily injections of high doses of PRL (1 mg/kg) in hypophysectomized dogs caused a rise in basal blood sugar and a diminished sensitivity to injected insulin; the glucose tolerance, however, was not impaired [12]. In hypophysectomized and adrenalectomized dogs or in partially depancreatized animals ovine PRL produced overt diabetes [13]. However, in a recent study Renauld et al. [14] were not able to demonstrate any significant "anti-insulin" effects of chronic PRL administration in the normal dog. A similar finding was made in hypophysectomized rats treated with ovine PRL [15].

The significant alterations in glucose metabolism after long-term endogenous hyperprolactinaemia seen in our investigation might be explained by increased gluconeogenesis in the liver, enhanced peripheral resistance to insulin and/or altered response of the pancreatic B-cell to glucose loading. Rathgeb et al. [2] showed increased hepatic glucose output in normal dogs treated with PRL. In their study, however, plasma glucose was virtually unchanged due to a concomitant stimulation of glucose uptake by peripheral tissues under PRL treatment. Plasma insulin levels were not altered. Therefore this mechanism seems not to be the exclusive one in hyperprolactinaemic patients.

Since PRL induces a rise in plasma free fatty acids in the dog [16] as well as in man [4] the impairment of the glucose tolerance seen in our patients might be due to the known inhibitory effect of elevated free fatty acids on peripheral glucose uptake. This hypothesis remains to be tested.

The possibility that the hyperinsulinaemia seen in our patients is due to a direct effect of PRL on the B-cell remains to be confirmed especially since Rathgeb et al. [2] did not find any changes in plasma insulin

during PRL administration. Our in vitro experiments suggest that a short exposure of the pancreas to prolactin did not change the beta cell sensitivity to glucose. They do not, however, rule out an effect of prolonged exposure to high PRL levels on the pancreas. Different effects occuring with short- and long term administration of growth hormone, a polypeptide chemically and biologically closely related to PRL, have been reported [17, 18].

The striking reduction of glucose-induced insulin release in hyperprolactinaemic patients treated with CB 154 is probably due to a suppression of the PRL levels and not due to an influence of CB 154 on insulin release at the pancreatic level. This view is supported by our perfusion experiments, in which CB 154 in pharmacological doses had no significant influence on glucose-stimulated insulin secretion. Treatment of healthy volunteers (n=5) with CB 154 (8 mg daily for 7 days) had no influence on glucose tolerance and insulin release. This is in agreement with data from del Pozo et al. [19].

The present findings might be of therapeutic importance, since suppression of the release of diabetogenic hormones like hGH and hPRL with bromocriptine in endocrine disturbances like acromegaly [20], hyperprolactinaemia or juvenile-type diabetes mellitus (Landgraf et al., unpublished observation) might improve the metabolic disturbances seen in these patients.

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