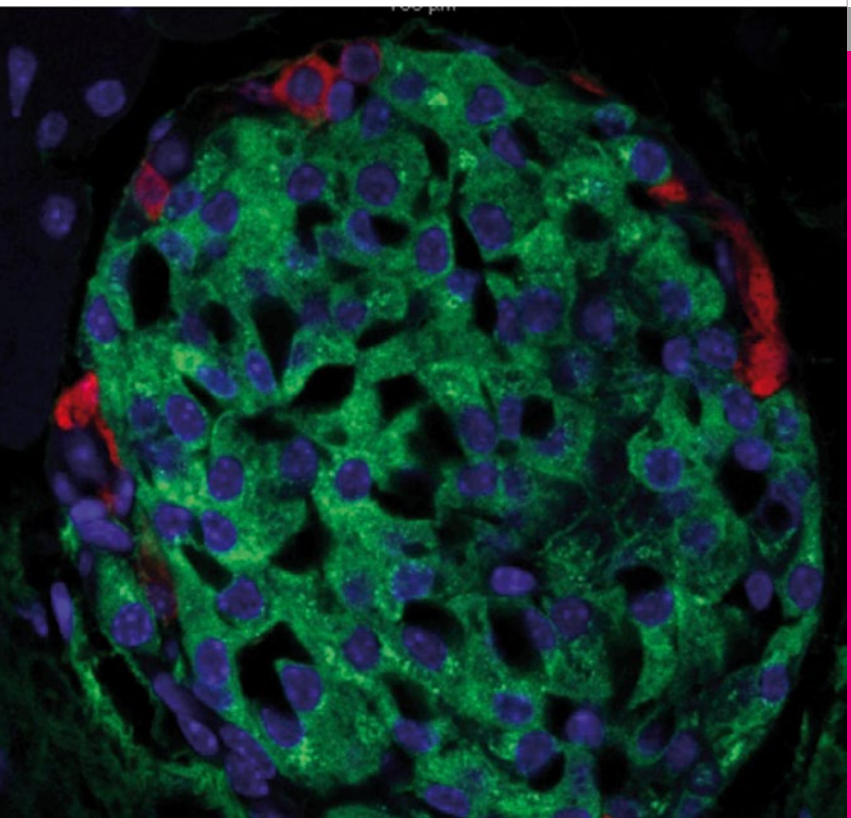
SWISS SOCIETY OF NEONATOLOGY

Winner of the Case of the Year Award 2012

Congenital hyperinsulinism



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INTRODUCTION

Congenital hyperinsulinism (CHI) is characterized by inappropriate secretion of insulin by the ß cells of the islets of Langerhans and is an extremely heterogeneous condition in terms of clinical presentation, histological subgroups and underlying molecular biology.

Histologically, CHI has been classified into two major subgroups: diffuse (affecting the whole pancreas) and focal (being localized to a single region of the pancreas) disease. Advances in molecular genetics, radiological imaging techniques (such as fluorine-18 L-3,4-dihydroxyphenylalanine-PET-CT (^{18F}DOPA-PET-CT) scanning) and surgical techniques have completely changed the clinical approach to infants with severe congenital forms of hyperinsulinemic hypoglycemia.

CASE REPORT

This male infant was born to a healthy 35-year-old G3/P3 by spontaneous vaginal delivery at 38 4/7 weeks. His birth weight was 3530 g (P 50-75), his head circumference was 35 cm (P 25) and his length was 50 cm (P 25-50). Postnatal adaptation was normal with an arterial cord pH of 7.28 and Apgar scores of 8, 9, and 9 at 1, 5, and 10 minutes, respectively. Pregnancy had been uneventful without any evidence of gestational diabetes.

On the second day of life, he was noted to have a grayish skin color and poor muscle tone. A POCT

blood glucose measurement indicated a glucose concentration of 0.1 mmol/l, which only increased to 0.4 mmol/l after the administration of oral glucose solution. At that point, our neonatal transport team was called. On arrival, intravenous access was established, blood cultures were obtained and a bolus of 2 ml/kg of a 10% dextrose solution was given, followed by a continuous glucose infusion at a rate of 5 mg/kg/min. He was started on antibiotics and transferred to our neonatal intensive care unit.

On transport, there was focal tonic-clonic seizure activity involving the right arm. Blood glucose concentration at that time was 3 mmol/l. Phenobarbital was started and the seizures did not reoccur. Antibiotics were discontinued after 72 hours. The further hospital course was remarkable for recurrent hypoglycemic episodes despite increasing rates of enteral and parenteral glucose administration (up to 18 mg/kg/min). High insulin concentrations were documented repetitively during episodes of hypoglycemia without concurrent increase in free fatty acids or ketone bodies. Cortisol and growth hormone responses, however, were adequate. Thus, a diagnosis of hyperinsulinemic hypoglycemia was made.

At the age of one month, the patient was transferred to the University Children's Hospital of Zurich for further management. The patient did not respond to a trial with the potassium channel activator diazoxide.

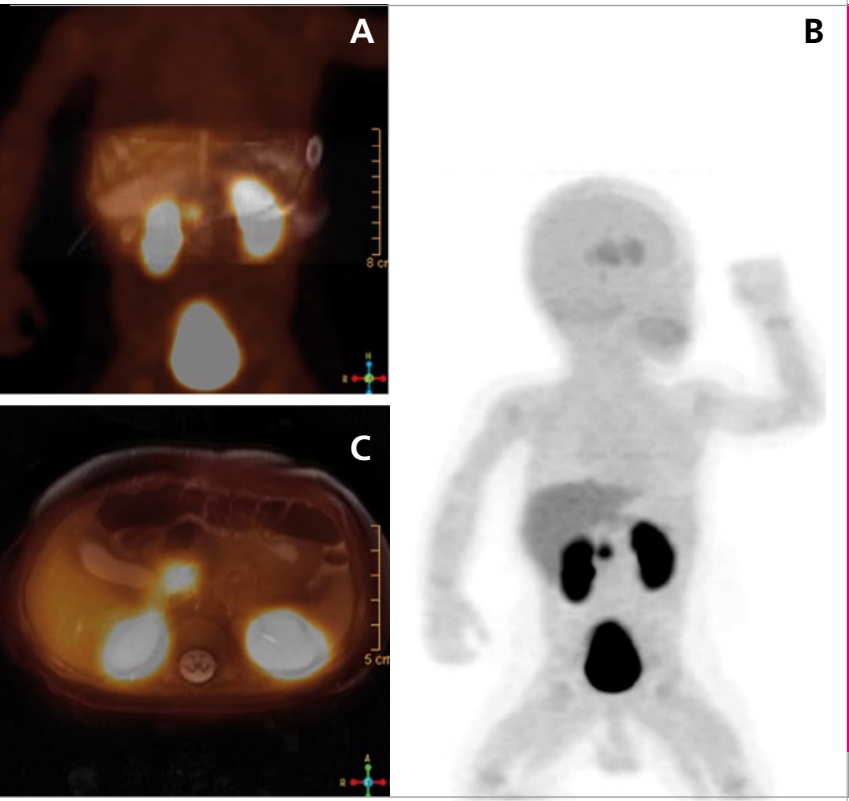


Fig. 1

Enhanced activity in the head of the pancreas (A, B: frontal view, C: coronal view); in addition, there is enhancement over the kidneys and bladder.

One week later, he was started on octreotide, initially by bolus injections but eventually by continuous subcutaneous infusion. At the age of seven weeks, he was discharged home fully breastfed on octreotide at a rate of 17 mcg/kg/day.

At the age of 4 months, MR studies of the head and abdomen were normal. Shortly thereafter, an ^{18F}DOPA-PET-CT scan was obtained. This study revealed increased focal activity in the region of the pancreatic head (Fig. 1, 2). At this time, a curative resection of the focal abnormality in the region of the pancreatic head was not scheduled because the parents were satisfied with the medical management and because of the considerable risks involved with a surgical approach. However, after several episodes of gastroenteritis with concurrent hypoglycemia, and after obtaining a second opinion at the University of Greifswald in collaboration with the University of Magdeburg and the Diagnostic Therapeutic Centre Frankfurter Tor in Berlin, Germany (a team that specializes in congenital hyperinsulinism) the parents opted for the operation. At the age of 16 months, a resection of the pancreatic head with preservation of the duodenum using a Roux-en-Y approach was performed (Fig. 3). Histology revealed hyperplasia of the islet cells without signs of malignancy (Fig. 4, 5).

Following the intervention octreotide was no longer required. No further episodes of hypoglycemia were

noted and regular glucose measurements were no longer necessary. Today, at the age of three years, the patient is cured without neurological deficits (Fig.6).

^{18F}DOPA-PET-CT*: Focus located in the head of the pancreas adjacent to the superior mesenteric vein (measuring 13.5 mm in diameter).*

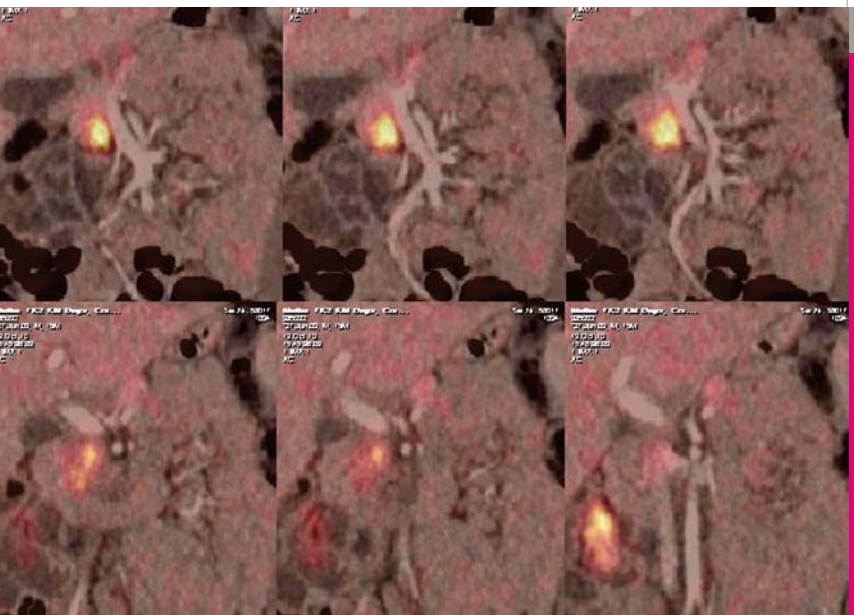


Fig. 2

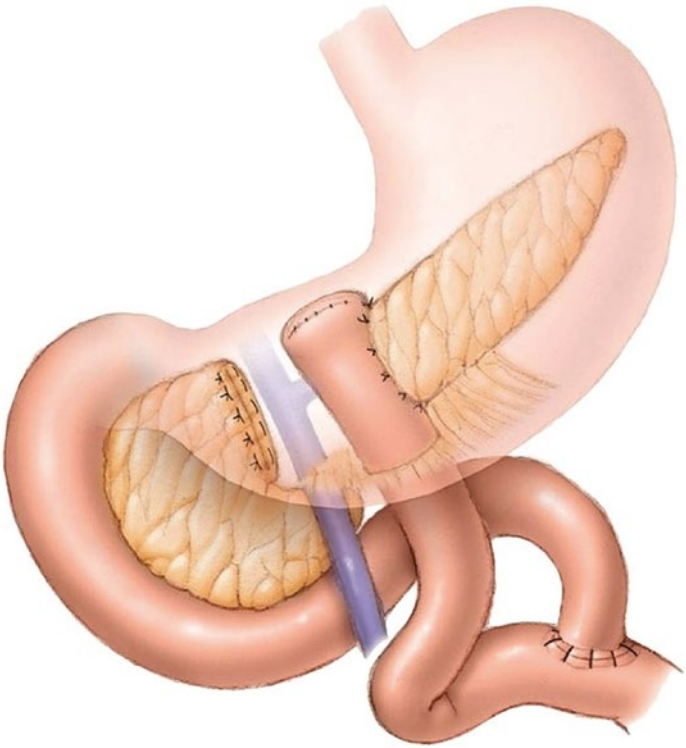


Fig. 3

Schematic drawing of the surgical procedure with excision of the focal lesion and reconstruction using a Roux-en-Y loop (note: in our patient, the excision was located in the head of the pancreas).

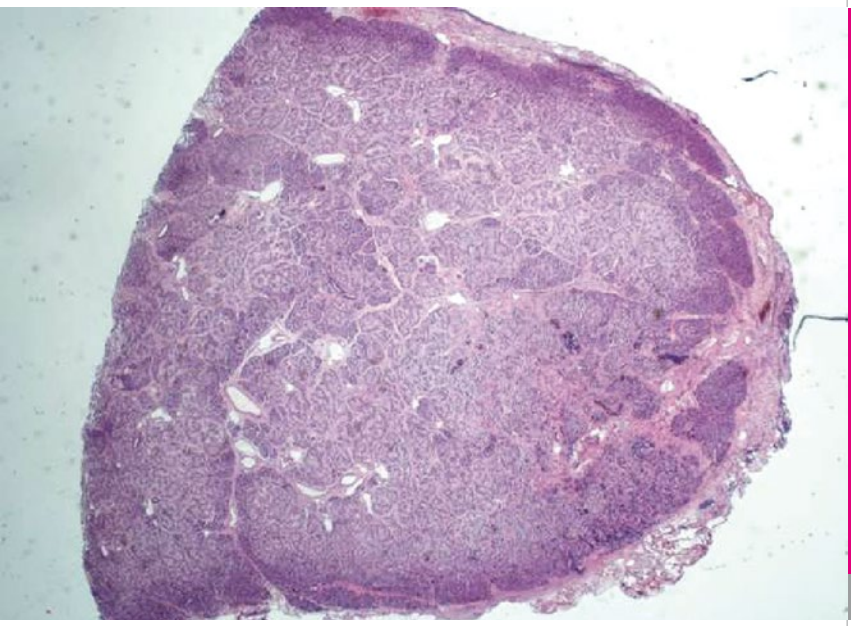


Fig. 4

Focal adenomatous hyperplasia with hyperplastic but normally structured islet and a peripheral rim of non-ß cells (HE stain).

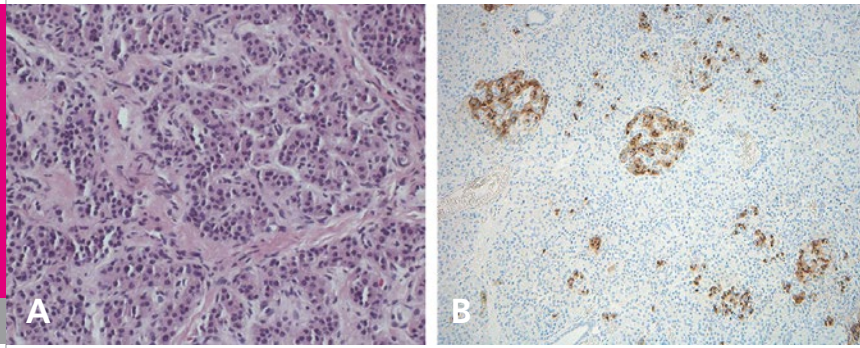


Fig. 5

Focal adenomatous hyperplasia: within the lesion, the ß cells are hyperactive, with enlarged cytoplasm and a large Golgi region full of proinsulin but relatively few insulin granules and little insulin labelling because the lesion hypersecretes but does not store insulin (A: HE stain, B: immunohistochemistry staining for proinsulin).

Fig. 6

Patient at the age of 3 years: normal psychomotor and cognitive development.

DISCUSSION

Hyperinsulinemic hypoglycemia (HH) occurs as a consequence of unregulated insulin secretion from pancreatic ß cells. This is the major cause of persistent and recurrent hypoglycemia in the neonatal and infancy period. Rapid diagnosis and appropriate management of these patients is essential to prevent brain injury, as HH is associated with a high risk of epilepsy, cerebral palsy and neurological handicap. Inappropriate insulin secretion drives glucose into insulin-sensitive tissues (such as skeletal muscle, adipose tissue and the liver) and simultaneously inhibits glucose production via glycolysis and gluconeogenesis, suppresses fatty acid release and ketone body synthesis (i.e., inhibition of lipolysis and ketogenesis). This metabolic „footprint" of insulin action (hypoglycemia with inappropriately low fatty acid and ketone body formation) explains why patients with HH have an increased risk of brain injury. The brain is not only deprived of its most important substrate (i.e., glucose) but also ketone bodies, which form an alternative source of fuel (1).

HH may be congenital (CHI, congenital hyperinsulinism), secondary to certain risk factors (such as maternal diabetes, perinatal asphyxia or intrauterine growth restriction) or it can be associated with developmental syndromes (such as Beckwith-Wiedemann syndrome).

CHI is a genetically heterogeneous disease with mutations having been described in 8 different genes (ABCC8, KCNJ11, GLUD1, GCK, HADH, HNF4A, UCP2 and SLC16A1) (2, 3). Although dominant mutations have been

reported in a number of these genes, recessively inherited CHI is more common. The estimated incidence of CHI in the general population is 1:30'000 to 1:50'000 but it increases to 1:2500 in communities with high rates of consanguinity (1). Mutations in the ABCC8 (ATP-binding cassette, sub-family C, member 8) and KCNJ11 (potassium inwardly rectifying channel, sub-family J, member 11) genes that encode the ATP-sensitive potassium channels (K_{ATP} channels) in the pancreatic ß cells are by far the most common cause of CHI and are estimated to account for 40-45% of all cases, whereas mutations in the remaining 5 genes are identified in approximately 5-10% of cases. The genetic etiology for the remaining 45-55% of patients remains unknown (2).

K_{ATP} channels play a central role in the regulation of insulin secretion in the pancreatic ß cells. The channels couple glucose metabolism to membrane electrical activity and insulin release. When glucose is metabolized by the ß cells the intracellular ratio of ATP/ADP increases and leads to closure of the channels; this results in cell membrane depolarization, Ca^{2+} influx via voltage-gated calcium channels and insulin exocytosis (1) (Fig. 7). CHI is associated with loss-of-function K_{ATP} channel mutations.

There are two main histologic subtypes of CHI: diffuse (60-70% of patients) and focal (30-40% of patients) (Fig. 8). Focal pancreatic lesions appear as small regions of islet adenomatosis measuring 2-10 mm in diameter,

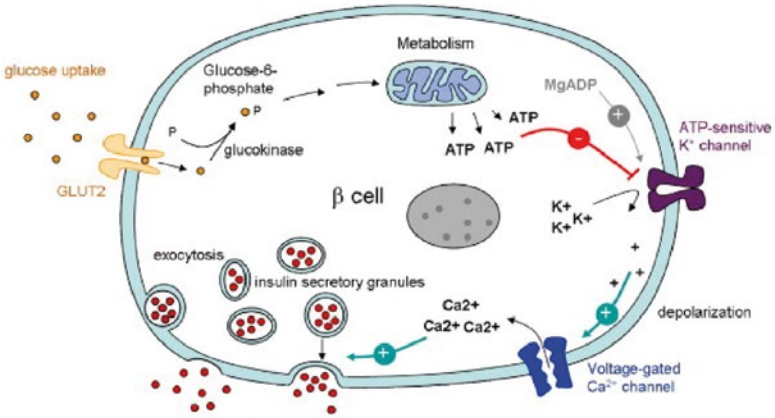


Fig. 7

Pancreatic ß-cell metabolism in response to glucose uptake. After glucose has entered the cell via the GLUT2 transporter, a phosphate moiety is added to the glucose molecule which then is metabolized in the mitochondria. The ATP produced competes with MgADP and closes the K_{ATP} channel. The subsequent depolarization opens the voltage-gated Ca^{2+} channels and entrance of Ca^{2+} in turn triggers exocytosis of the insulin secretory granules (from Ref.7).

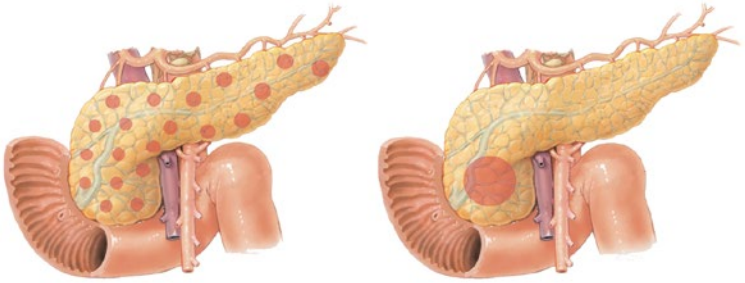
which are characterized by ß cells with enlarged nuclei surrounded by normal tissue. In contrast, diffuse pancreatic disease affects all the ß cells within the islets of Langerhans (1). The focal form of CHI exhibits a particular genetic pattern with a paternally inherited mutation on chromosome 11p15.1 and a loss of the maternal allele specifically in the cells of the focal lesion (4). The majority of patients with diffuse disease have homozygous or compound heterozygous mutations in ABCC8 and KCNJ11.

Advances in diagnostic imaging have revolutionized the ability to localize lesions in the pancreas by the introduction of integrated ^{18F}DOPA-PET-CT that merges anatomical and functional data. L-DOPA is adsorbed by neuroendocrine and pancreas islet cells and metabolized into dopamine. Beta cells of the pancreas possess dopamine receptors. The uptake of ^{18F}DOPA is considerably increased in foci with high insulin synthesis rates. It is not only possible to differentiate between diffuse and focal forms with high sensitivity and specificity, but localization of the focus can also be provided with a formerly unthinkable precision of up to a few millimetres (5).

The goal of treatment in infants with CHI is to maintain plasma glucose levels > 4 mmol/l. Long-term treatment with diazoxide has dramatically reduced the need for extensive surgical procedures. Diazoxide acts by keeping the K_{ATP} channel open, thereby preventing depolarisation of the ß cell membrane and insulin secretion.

In patients unresponsive to diazoxide, it is essential to differentiate focal from diffuse disease, as the surgical approaches are radically different. In patients with focal disease, precise preoperative localization and limited surgical excision „cures" the patient. In contrast, patients with diffuse disease may require a near-total pancreatectomy, which will have lifelong implications (high risk of diabetes mellitus and/or pancreatic exocrine insufficiency).

Other medical treatments that can be used while awaiting surgical treatment include octreotide, glucagon, and continuous intragastric dextrose administration. Octreotide is the second line of medical therapy for infants with CHI who are unresponsive to diazoxide. Octreotide is a long-acting somatostatin analogue that inhibits insulin secretion by inducing hyperpolarization of ß cells and by direct inhibition of voltage-dependent calcium channels. Long-term medical management of diffuse disease with subcutaneous octreotide administration should not be taken lightly as it may impose a huge burden and is extremely stressful on the family. Glucagon can be given as a continuous intravenous infusion to help maintain euglycemia in infants who are awaiting surgery. Unfortunately, glucagon is too unstable in solution to be useful for chronic management (1, 6). Fig. 9 outlines various treatment options in patients with CHI.



A B

Fig. 8

Diffuse CHI (A) involves the entire pancreas while the focal form (B) is localized to a single region of the pancreas (from MediVisuals.inc).

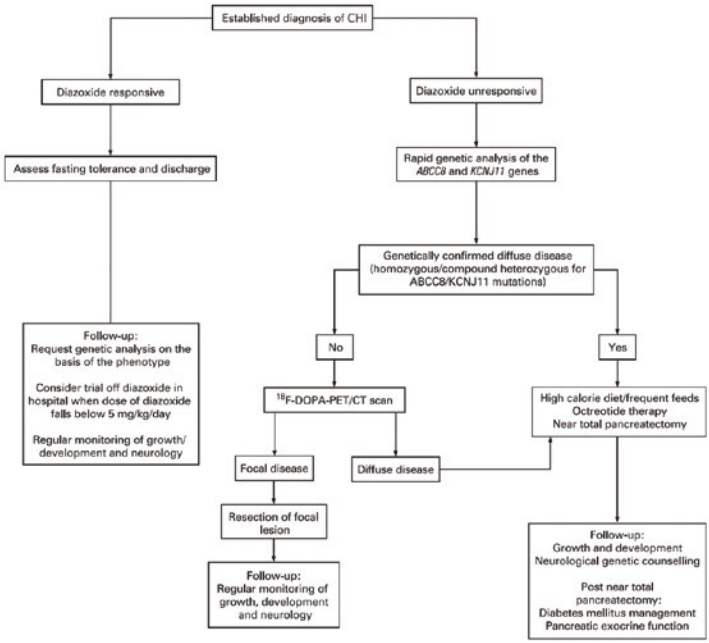


Fig. 9

Flow chart outlining the management cascade of neonates with hyperinsulinemic hypoglycemia (CHI). Clinically, CHI can be classified into diazoxide-responsive and diazoxide-unresponsive disease. A ^{18F}DOPA-PET-CT *scan is currently only indicated in neonates who are unresponsive to diazoxide and do not have genetically confirmed diffuse disease.*

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