TITLE

Long-term follow up of Children with Congenital Hyperinsulinism on Octreotide Therapy

Huseyin Demirbilek[1], Pratik Shah[1], Ved Bhushan Arya [1], Louise Hinchey[1],
Sarah E. Flanagan[2], Sian Ellard[2], Khalid Hussain[1]

[1]Developmental Endocrinology Research Group, Clinical and Molecular Genetics Unit, Institute of Child Health, University College London, 30 Guilford Street, London WC1N 1EH, UK

Department of Paediatric Endocrinology, Great Ormond Street Hospital for Children, London WC1N 3JH, UK.

[2]Institute of Biomedical and Clinical Science, University of Exeter Medical School, Exeter EX2 5DW, UK

OBJECTIVES

Congenital hyperinsulinism (CHI) is an important cause of persistent and severe hypoglycemia in the neonatal, infancy and childhood periods. Octreotide, a somatostatin analogue, is commonly used in diazoxide unresponsive congenital hyperinsulinism (CHI) patients as a second line medication. The aim of this study was to evaluate the dose range, side effects and long-term follow up in a large cohort of CHI patients on multiple daily octreotide injections.

METHODS

This retrospective study was carried out in the department of Paediatric Endocrinology at Great Ormond Street Hospital for Children, London. CHI patients who were unresponsive to maximum dose of diazoxide (20 mg/kg/day) and subsequently received octreotide therapy (5-35 µg/kg/day) since November 2001 were included in the study. Patients who could not be weaned off intravenous dextrose fluids after starting octreotide therapy went onto have further investigations like pancreatic venous sampling or 18F-DOPA PET CT. Depending upon the subtype of CHI, these patients either underwent near-total pancreatectomy or focal lesion resection/partial pancreatectomy. Post-pancreatectomy, octreotide therapy was recommenced on those who continued to have hypoglycemia. The case-notes of the patients treated with octreotide between November 2001 and December 2013 were retrospectively reviewed to collect detailed clinical and biochemical characteristics on presentation, molecular genetic analysis results, requirement for pancreatectomy and doses and duration of octreotide therapy used. Baseline hepatobiliary ultrasound, thyroid function test, growth factors (insulin like growth factor 1 -IGF1 and IGF binding protein 3 -IGFBP3), and liver function tests were performed before commencing octreotide therapy. These investigations were repeated at regular 3-6 monthly intervals to identify adverse effects of octreotide therapy. Weight and length/height was measured at the time of presentation and then every clinic appointment and admission to our investigation unit.

Effects of Octreotide therapy on liver function and gall bladder

Apart from mild gastrointestinal side effects such as abdominal discomfort, diarrhoea, and transient elevation of liver transaminases, no serious side effects were observed which resulted in withdrawal of treatment. Transient elevation of liver enzymes was observed in 13 patients (46.4%), which resolved within 4-8 weeks despite continuing octreotide. In total, the rate of having elevated liver enzyme in patients who had gall bladder pathology (n=4/9, 44.4%) and without gall bladder pathology (n=9/19, 47.4%) were not statistically different (p=0.604). Also, there was no difference in the mean dose of octreotide in patients with and without elevated liver enzymes (17.7±7.5 µg/kg/day v/s 17.8±7.7 µg/kg/day; p=0.969), However median age at which octreotide therapy was commenced was significantly lower in patients with elevated liver enzymes as compared to those with normal liver enzymes (0.25 months v/s 1.5 months; p=0.046).

Gall bladder pathology was observed on follow up hepatobiliary ultrasonography in 9 (32.1%) patients (gallstones – 6; gall bladder sludge – 3) (Table 2). These patients were treated with ursodeoxycholic acid (UDCA). There was no statistical significant difference between the mean doses of octreotide in patients with or without gallstones formation (18.8±7.7 µg/kg/day v/s 17.3±7.5 µg/kg/day respectively, p=0.635). The mean duration of developing gall bladder pathology (gallstone or sludge) on octreotide therapy was 4.3±4.6 months in 9 patients, whilst 19 patients without gall bladder pathology have been followed up for 53.6±32.9 months. Also there was no statistical significant difference between median age of commencing octreotide therapy in patients with or without gallbladder pathology (1.0 months v/s 0.5 months; p=0.783).

Effects of octreotide therapy on weight, linear growth and pituitary functions

Serial evaluation of height-SDS during follow up over a year on last admission revealed short stature (height lower than -2 SDS but within the target centile range for the family) in 3/28 (10.7%) patients. All these three patients had familial short stature. Two of these had normal height velocity and serum and IGFBP3 levels within normal range for age and sex. The third patient with low serum IGF1 and IGFBP3 levels was investigated with growth hormone stimulation test and overnight growth hormone profile, both of which were normal. On comparison of serum IGF1 and IGFBP3 levels before and after octreotide therapy (range: 6 months to 9.5 years), there was no statistical significant reduction in the values of IGF1, and IGFBP3 (Figure 2). Median (interquartile range) for serum IGF1 SDS measured before octreotide therapy vs. follow up measurement were -0.6 (0.7) vs. -0.4 (0.6) (p=0.986) and for serum IGFBP3 SDS were -0.1 (1.7) vs. -0.5 (1.4) (p=0.121) respectively (Figure 1). On their recent evaluation, mean BMI z-score was 1.3±0.9 (range: -1.0 to 2.6). Seven out of 28 (25%) patients had a BMI z-score> 2 SD.

RESULTS

Between 2001 and 2013, 28 diazoxide unresponsive CHI patients (17 males and 11 females) received long-term octreotide therapy. CHI was diagnosed at a median age of 1 week (range: 1-80 weeks). The clinical and biochemical characteristics at the time of the diagnosis are summarized in Table 1. Genetic analysis identified 29 different *ABCC8/KCNJ11* mutations in 25 patients (*ABCC8* – 22, *KCNJ11*- 3). Of these, 15 were bi-allelic mutations and 10 were mono-allelic mutations.

Table 1: Clinical and biochemical characteristics of CHI patients at the time of the diagnosis

	Mean±SD (Range)
Age of diagnosis (weeks)*	**1 (1-80)**
Birth weight (Kg)	**4.0±0.8 (2.5-6.0)**
Gestation at birth (weeks)	**37.5±2.4 (33-40)**
Glucose (mmol/L)	**1.9±0.8 (0.1-3.0)**
Insulin (mU/L)	**31.4±39.1 (2.3-174)**
c-peptide (pmol/L)	**584.2±517.7 (173-1786)**
Growth hormone (mcg/L)	**19.7±16.6 (2.5-59.3)**
Cortisol (nmol/L)	**346.7±272.7 (56-915)**
Ammonia (mmol/L)	**33.6±13.9 (15-59.5)**
Lactate (mmol/L)	**1.6±0.7 (0.8-3.6)**
***ABCC8/KCNJ11* mutations**	
Biallelic	**15**
Monoallelic	**10**
No *ABCC8/KCNJ11* mutations	**3**

*Median (min-max)

Octreotide in combination with frequent carbohydrate rich daytime feeds and continuous intragastric overnight feeds provided a successful management strategy without need for surgery in 12 out of 28 (42.8%) patients (Figure 1). There was no statistically significant difference in the rate of octreotide responsiveness between patients with mono-allelic (4/10, 40%) or biallelic (6/15, 40%) K_{ATP} channel mutations (p=0.622). In 16 patients where octreotide therapy failed to maintain normoglycemia pancreatectomy was performed (14 had near total pancreatectomy and 2 had focal resection). From those, 12 patients required subsequent octreotide therapy post pancreatectomy, 3 patients developed diabetes mellitus and one patients have been cured. Percutaneous gastrostomy was performed in 23 out of 28 patients (82.1%) to provide adequate calorie-carbohydrate intake and overnight bolus feeds. The mean dose of octreotide commenced was 17.8±7.5 µg/kg/day (range: 7.5-33.7 µg/kg/day). The mean duration of follow up under octreotide therapy was 52.4±33.8 months (range: 6 months to 9.5 years).

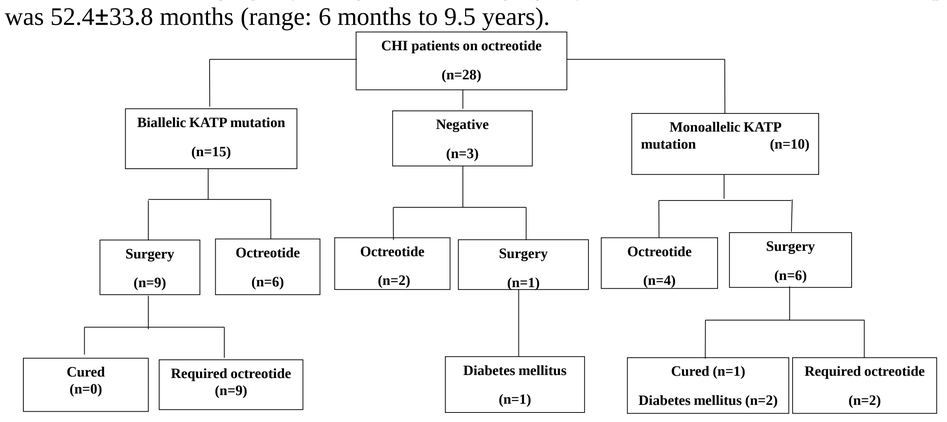

Figure 1. A summary of genetic background, treatment and follow up characteristics of our cohort.

The mean free T4 was 14.3±1.8 pmol/L (range: 11.7-19) and mean TSH was 2.2±1.1 mU/ L (range: 0.7-4.1). During follow up there was no documented hypothyroidism in any patients on octreotide therapy. Octreotide was commenced in the neonatal period in 15/28 (53.6%) patients and no episodes of necrotizing enterocolitis were observed in our cohort.

Table 2: Characteristics of patients who had gall bladder pathology on hepatobiliary ultrasound

Age at diagnosis	**Gene**	**Protein description**	**DNA description**	**Pathology**	**Age octreotide started***	**Age when pathology detected***	**Octreotide dose#**	**Duration to develop***	**Treatment**	**Clinical and Laboratory features**	**Age last admission**	**Octreotide dose##**	**Follow up**
3 weeks	***ABCC8***	**p.E128K/p.E128K**	**c.382 G>A/c.382G>A**	**Gallstone**	**0.75**	**3**	**16**	**2**	**UDC**	**AS**	**3.2 years**	**13**	**Resolved in 5 months**
1 day	***ABCC8***	**p.G735E/R1215W**	**c.2204G>A/c.3643C>T**	**Gallstone**	**1.5**	**5.5**	**25**	**4**	**UDC**	**AS**	**5.6 years**	**25.6**	**Resolved in 3.5 years**
1 day	***ABCC8***	**p.R74W/N**	**c.220C>T/N**	**Gallstone**	**1**	**3.5**	**11.5**	**2.5**	**UDC**	**AS , transient elevation of transaminases**	**9 months**	**30**	**Resolved in 2.5 months**
1 day	***ABCC8***	**p.G1485E/N**	**c.4454G>A/N**	**Gallstone**	**2.5**	**3.0**	**28.5**	**1**	**UDC**	**AS**	**8.2 years**	**22.6**	**Stable for 7.6 years**
1 day	***ABCC8***	**p.A315fs/p.A315fs**	**c.945delC/c.945delC**	**Gallstone**	**3**	**11.5**	**11**	**10**	**UDC**	**AS , transient elevation of GGT**	**7 years**	**15**	**Stable for 6 years**
1 day	**ABCC8**	**p.?/N**	**c.3992-9G>A/N**	**Gallstone**	**0.25**	**15.0**	**15**	**14.5**	**UDC**	**AS, transient elevation of transaminases**	**9.5 years**	**6.6**	**Stable for 8.2 years**
1 day	**Negative**	**Loss of heterozygosity in pancreatic tissue**		**Sludge**	**0.25**	**1.5**	**NA**	**1**	**UDC**	**AS**	**6 months**	**-**	**Resolved in 1 months**
4 weeks	***ABCC8***	**p.M429X/N**	**c.1254_1284dup/N**	**Sludge**	**1.5**	**5.5**	**30**	**3**	**UDC**	**AS**	**9 months**	**30**	**Stable for 3 months**
1 day	***ABCC8***	**p.I1425L**	**c.4273A>C/N**	**Sludge**	**0.25**	**1**	**13.8**	**1**	**UDC**	**AS , transient elevation of transaminases and conjugated bilirubinemia**	**2.6 years**	**15**	**Stable for 2.5 years**

*Months, Octreotide dose (µg/kg/day) #when gall bladder pathology detected first and ##at last admission, UDC: Ursodeoxycholic acid, AS: Asympthomatic, NA: Not available

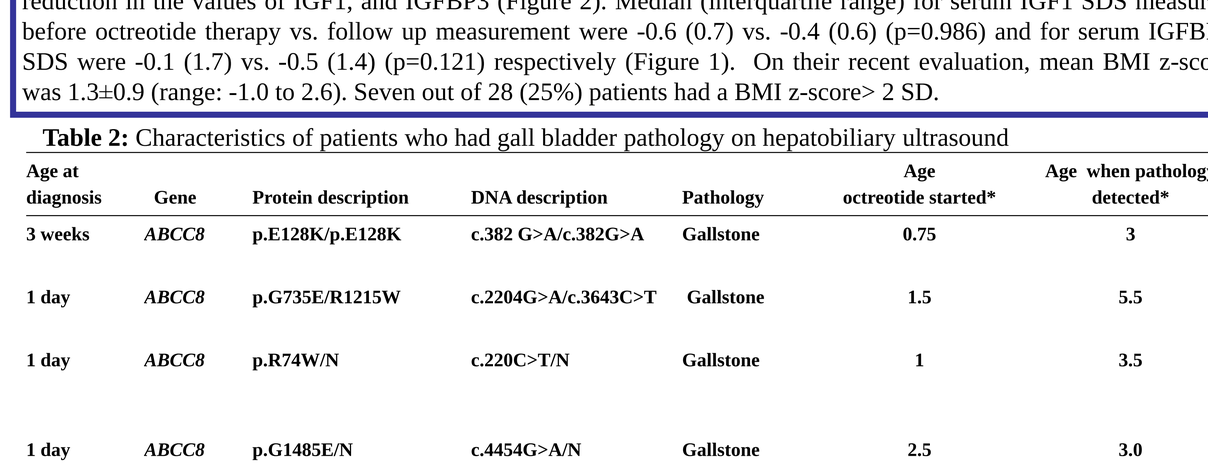

Figure 2: Evaluation of IGF1 and IGFBP3 values measured before octreotide therapy and during follow up on octreotide therapy did not showed any statistically significant suppression.

CONCLUSIONS

This is the largest study to our knowledge evaluating long term follow up of CHI patients on octreotide therapy. We showed that most prevalent side effects were gall bladder pathology (gall stone or sludge) and transient elevation of liver enzymes. More than half of patients with gall bladder pathology had normal liver function test. Duration and dose of octreotide did not have any correlation with the development of gallstone. Side effect on pituitary function such as arrest of linear growth, decrease in IGF1 and IGFBP3 levels and hypothyroidism was not found clinically significant. Although octreotide is a safe and effective alternative therapy option for diazoxide unresponsive CHI patients, patients on octreotide therapy should be followed up closely for octreotide side effects regardless of the dose and duration of therapy.