# Sotos Syndrome presenting with Neonatal Hyperinsulinaemic Hypoglycaemia, Extensive Thrombosis and Multisystem Involvement

Manuela Cerbone[1], Emma Clement[2], Martin McClatchey[3], Joanna Dobbin[3], Clare Gilbert[1], Morgan Keane[3], Lamia Boukhibar[4], Hywel Williams[4], Andrey Gagunashvili[4], Mehul T Dattani[1,5], Jane Hurst[2], Pratik Shah[1]

*[1] Department of Endocrinology, Great Ormond Street Hospital for Children NHS Foundation Trust, [2]Department of Clinical Genetics, Great Ormond Street Hospital for Children NHS Foundation Trust, [3]Department of Paediatrics, Barking Havering & Redbridge Trust, [4]GOSgene, Genetics and Genomic Medicine, UCL Great Ormond Street Institute of Child Health London, [5] Section of Genetics and Epigenetics in Health and Disease, Genetics and Genomic Medicine Program, UCL GOS Institute of Child Health London*

**Short running title:** Extended phenotype of Sotos syndrome

**Corresponding author:**

Dr Pratik Shah

Consultant Paediatric Endocrinologist and Honorary Clinical Lecturer

Great Ormond Street Hospital for Children and UCL GOS Institute of Child Health

Great Ormond Street, London WC1N 3JH

Tel: 02074059200 Ext 8296

Email: pratik.shah@gosh.nhs.uk

**ESPE membership:** MC, MTD and PS are ESPE members

**Key words:** Sotos syndrome**,** Congenital Hyperinsulinaemic hypoglycaemia**,** Thrombosis**,** Liver dysfunction, Rapid Whole Genome Sequencing

**Funding source:** The Rapid Whole Genome Sequencing (WGS) was funded by NIHR GOSH/UCL BRC: ormbrc-2012-1.

**ESTABLISHED FACTS**

- Congenital hyperinsulinism can be the presenting feature of Sotos syndrome

**NOVEL INSIGHTS**

- Patients with Sotos syndrome can require diazoxide treatment beyond the neonatal period (and up to 8 months of age)
- Extended phenotype of Sotos syndrome presenting with congenital hyperinsulinaemic hypoglycaemia might include thrombosis, cerebrovascular events and liver dysfunction
- In complex genetic cases presenting in the neonatal period with incomplete/overlapping phenotypes, broad genomic testing may be a useful diagnostic strategy

**ABSTRACT**

Initially described as an uncommon presenting feature of Sotos Syndrome (SoS), over the last decades, Congenital Hyperinsulinaemic hypoglycaemia (CHI) has been increasingly reported in association with this condition. The mechanism responsible for CHI in SoS is unclear.

We report the case of a neonate presenting with CHI and extensive venous and arterial thrombosis associated with kidney, heart, liver, skeleton and brain abnormalities and finally diagnosed with SoS on whole genome sequencing.

Our case describes an extended phenotype associated with SoS presenting with CHI (including thrombosis and liver dysfunction) and reinforces the association of transient CHI with SoS. The case also shows that an early neonatal diagnosis of rare genetic conditions is challenging, especially in acutely unwell patients, and that in complex cases with incomplete, atypical or overlapping phenotypes, broad genomic testing by whole exome or whole genome sequencing may be a useful diagnostic strategy.

**BACKGROUND**

Congenital Hyperinsulinaemic hypoglycaemia (CHI), a condition of inappropriate insulin secretion leading to profound hypoglycemia, can be found in isolation or, more rarely, as part of a genetic syndrome. Some genetic conditions such as Beckwith-Wiedemann Syndrome (BWS) are known to be associated with CHI [1]. However, over the last decades, CHI has been described in several other syndromes [2], including Sotos (SoS) [3-5]. SoS (MIM 117550) is an overgrowth syndrome characterized by distinctive facial features, developmental delay, behavioural problems, heart, kidney and brain involvement, scoliosis, hearing and vision loss. A heterozygous mutation in NSD1 (MIM 606681) can be identified in more than 75% of cases [6]. The mechanism responsible for CHI in SoS remains unclear. We report the case of a neonate presenting with severe CHI and extensive thrombosis associated with kidney, heart, liver, skeleton and brain abnormalities and diagnosed with SoS on Whole Genome Sequencing (WGS).

**CASE PRESENTATION**

A term male baby (gestational age: 41+3 weeks; birth weight 3.770 kg, 0.16 SDS; head circumference 35 cm, 0.43 SDS), first child of non-consanguineous caucasian parents, was born in good condition (APGAR 9 at 1 min, 9 at 5 mins, 9 at 10 mins) by emergency caesarean-section in view of a pathological cardiotocography trace. Antenatal scans had revealed an arachnoid cyst and a right duplex kidney but the pregnancy had been otherwise uncomplicated. He was found to be hypoglycaemic (blood glucose 1.1 mmol/l) and was admitted to the neonatal intensive care unit where he required high concentrations of glucose via a peripheral intravenous infusion (peak glucose infusion rate 14.5mg/kg/min), and was intubated for worsening respiratory distress.

*Physical Characteristics*

On examination, in the neonatal period, the baby was found to have pectus excavatum, bilateral overlapping 1st & 2nd and 3rd & 4th digits, a small umbilical hernia, single palmar creases and deep-set eyes. Neurologically he demonstrated abnormal posturing at rest, with flexed limbs and increased peripheral limb tone. There were large and small joints contractures with an arthrogryposis-like phenotype. Conversely, central tone was reduced and there was significant head lag and a paucity of spontaneous movements. During the first few months of life, the baby developed distinctive features including down-slanting eyes, a prominent forehead with frontal bossing, nasal bridge prominence and a long chin (Figure 1). The patient's growth pattern is shown in Figure 2.

*Systemic events*

On day 2 of life discrepancies were noted between lower limb pulses, with an impalpable right femoral pulse. Ultrasound demonstrated an extensive thrombus formation in the lower two-thirds of the inferior vena cava with occlusion of both iliac veins and a long segment of occlusion from the distal right-common artery to the middle of the right-external iliac arteries. On day 3 of life, he developed seizures associated with periods of apnoea (despite ventilation) for which he was treated with phenobarbitone and phenytoin. An electroencephalogram was normal and he did not show any further clinical seizure activity thereafter. Neuroimaging showed additional findings of a left middle cerebral artery infarct and later appearances were of cystic encephalomalacia in the left frontal, parietal and occipital regions, with a background of diffuse abnormal white matter signal and a thin corpus callosum. A thrombosis screen showed normal patient concentrations of protein C and S and normal maternal anti-phospholipid antibodies. The patient was initiated on low-molecular-weight heparin (LMWE) for the extensive thrombotic foci. Upon further imaging, he was confirmed to have a right duplex kidney and echocardiography demonstrated a small

patent foramen ovale (PFO). During the first weeks of life, he developed a progressive liver derangement with conjugated hyperbilirubinaemia, increased gamma glutamyltransferase and hepatic transaminitis (Table 1). The liver ultrasound showed normal hepatic structures and the blood investigations (α1 antitrypsin, cerulosplasmin and Gal-1-PUT) were negative. Spinal X-Ray (performed for suspicion of Alagille syndrome) was normal.

*Glycaemic control*

The initial screen for hypoglycaemia performed on day 3 of life showed the presence of inappropriately detectable insulin and C-Peptide, coupled with low non-esterified fatty acids and beta-hydroxybutyrate, leading to the diagnosis of CHI. The extended metabolic investigations and the counter-regulatory hormones were normal (Table 1). The patient was transferred from the tertiary Neonatal Intensive Care Unit to our tertiary Endocrine centre in view of difficulties in delivering high glucose concentrations via a peripheral cannula and inability to achieve a stable central venous access, in addition to the complex presentation with multisystemic involvement. A Hickmann line was urgently inserted on the night of admission (day 23 of life). During the following days the patient's glucose requirement improved, but, by day 28 of life, he had a persistent intravenous glucose requirement. Repeated diagnostic fast tolerance tests demonstrated undetectable insulin concentrations but detectable pro-insulin and c-peptide with low ketones (Table 1). On day 42 of life the patient was started on a low dose of diazoxide (2 mg/kg/day) with good response, allowing progressive reduction in intravenous fluid requirements and extended oral feed intervals.

*Diagnostic pathway*

Targeted next generation sequencing for known molecular causes of congenital hyperinsulinism did not identify a pathogenic mutation in *KCNJ11, ABCC8, GLUD1, GCK, HADH, HNF4A, INSR, SLC16A1, TRMT10A* and *HNF1A*. The association of coagulopathy, liver

and brain abnormalities, distinctive facial features and CHI raised the suspicion of a congenital disorder of glycosylation (CDG). However, transferrin electrophoresis was normal in two repeated samples (before and after 6 weeks of age). CDG enzyme testing was also normal. The combination of clinical features and multisystemic involvement made an underlying genetic aetiology likely but the differential diagnosis was wide. The patient underwent Rapid WGS as part of a research study (REC reference 08/H0713/82). This identified a de novo, pathogenic stop-mutation in *NSD1* (c.1873G>T; p.Gly625Ter), confirming a diagnosis of SoS. This result was confirmed in a diagnostic laboratory. The research WGS has not identified any additional likely pathogenic mutation associated with prothrombotic risk or CDG.

*Follow-up*

The patient continued to require a small dose of diazoxide, keeping the blood glucose stable until the age of 8 months. The central venous access was removed at the age of 6 months. At the age of 8 months, diazoxide was discontinued, his liver dysfunction had resolved, the PFO had closed and the patient completed a long course of LMWH with documented regression of his vascular thrombi. He is currently 12 months of age with a weight of 0.29 SDS, height of 2.76 SDS and head circumference 1.89 SDS (Figure 2). He is on a normal diet and he is able to fast overnight without developing hypoglycaemia. He remains under the care of multiple specialist teams and is requiring physiotherapy and occupational therapy for his associated anomalies, developmental delay and for his residual right hemiparetic features.

**DISCUSSION AND CONCLUSIONS**

CHI can be found in association with numerous syndromes (including BWS, Kabuki, Costello, Simpson-Golabi, Turner and Perlman) or metabolic conditions (such as CDG and

Hyperinsulinism/Hyperammonemia). Most of the syndromic forms of hyperinsulinism are characterized by diffuse (as opposed to focal) pancreatic disease and they are typically responsive to diazoxide [2]. Initially reported as an infrequent complication of SoS [7-10], over the last decade neonatal CHI has been increasingly described in this condition [3-5] with a recent Japanese national survey documenting CHI in 9/88 (10.2%) children with SoS and therefore suggesting that this is not an uncommon presenting feature of this condition [11]. The detailed clinical characteristics and biochemical mechanisms of CHI in SoS have not yet been well characterized. One reason for this could be that the classical distinctive SoS features of facial anomaly and overgrowth may be missed in the neonatal period and appear more gradually during childhood [6]. As such, with the diagnosis being made more commonly in childhood than infancy, there has been less emphasis in the reported literature on the previous history of transient hypoglycaemia. In some cases atypical features can also be present and further compound the diagnostic dilemma. Indeed, for our patient, the overgrowth and distinctive facial features were only mild at presentation and difficult to assess in an acutely unwell child. Additionally, the associated coagulopathy and liver phenotype pinpointed more toward a diagnosis of CDG. Hence, the diagnosis of SoS was not clinically suspected and was only revealed by rapid WGS. In a Japanese case series, the majority of SoS patients presented with early hypoglycaemia (within < 3 hours of life) with only 2/9 requiring diazoxide and only 1/9 needing treatment for > 2 months [11]. In another study from the same group, 5/5 SoS patients were treated with intravenous glucose infusion at a maximum rate of 4.6-11.0 mg/kg/min for 12-49 days. The hyperinsulinism resolved between 12 days and 6 weeks in 4/5 cases. Three out of 5 patients had associated cardiac abnormalities and all of them displayed some neuroimaging changes. Genito-urinary abnormalities were present in 4/5 patients [4]. Compared with the above reported cases,

the CHI features of our patient seem to be at the most severe end of the spectrum with a higher glucose requirement at presentation (14.5 mg/kg/min) and the need for treatment with diazoxide up to 8 months of age. Similarly to the other reported cases, our patient displayed associated renal, heart and brain abnormalities. Interestingly, in our case, the insulin concentrations at presentation were only mildly elevated and, subsequently, the insulin became undetectable but the C-peptide and pro-insulin were detectable with low blood ketones, and the patient was still requiring very high glucose concentrations suggestive of a hyperinsulinaemic status. These findings confirm that the degree of hyperinsulinism is not correlated with the severity of the CHI or the patient's glucose requirement [12]. They also suggest that some "insulin-like" activity should be suspected even in children with undetectable insulin concentrations when the hypoglycaemia is associated with detectable C-Peptide and/or Pro-insulin and low ketones [13]. Moreover, it is important to note that our patient responded to a very low diazoxide dose thus showing that lower than the standard adopted doses [2] might be adequate to revert the hyperinsulinaemic status and to guarantee the normoglycaemia in neonates/infants presenting with CHI. The pathophysiology of hyperinsulinism in SoS remains unknown. Asphyxia seems to be a common feature (33%) in syndromic forms of CHI [11], and hence it has been suggested that perinatal stress might contribute to the onset of hypoglycaemia [14]. However, not all children with SoS and CHI had asphyxia at birth and it has been hypothesized that disorders of NSD1 itself may cause abnormal secretion of insulin [3,4], although abnormalities in other genes responsible for the onset of CHI cannot be excluded. Whatever the underlying mechanism, the recognition that SoS is not uncommonly associated with CHI has important clinical consequences, as CHI is a well-known major risk factor for perinatal brain injury and subsequent neurodevelopmental disability [15].

Therefore, a rapid diagnosis and a prompt treatment of CHI in a condition like SoS, which is already associated with learning difficulties, is essential to prevent further brain damage. To our knowledge this is the first report of SoS presenting with CHI and extensive thrombosis and cerebrovascular accidents. It is well known that critically ill neonates, both term and preterm, are most vulnerable to development of venous and arterial thrombosis and they are at greatest risk of symptomatic thromboembolic disease [16], but the degree of thrombosis and the cerebral infarct displayed by our patient are difficult to explain with the perinatal stress only. Thrombosis has been identified in a significant proportion (19%) of patients with CHI and central venous access, with no association with putative risk factors (incidence of focal CHI, frequency of genetic mutations, maximum concentration of dextrose, glucagon infusion rate, duration of high concentration dextrose) [17]. However, in our patient, the detection of extensive venous and arterial lower limb thrombosis and cerebral artery infarction preceded the placement of the central venous access. Elevated fasting insulin concentrations have been independently associated with impaired fibrinolysis and hypercoagulability in subjects with normal glucose tolerance and with impaired fibrinolysis in subjects with glucose intolerance [18]. Hyperinsulinaemia is also a well-recognized independent risk factor for ischaemic heart disease [19]. Although it is not inconceivable to infer that the presence of hyperinsulinaemia and treatment with high dextrose concentrations might have contributed to the increased risk of thrombosis in our patient, a direct relationship between those risk factors and the onset of thrombosis in patients with CHI *without* central venous access has never been documented. Hence the aetiology of the extensive multisite thrombosis in our patient remains unclear. Additionally, the transient liver dysfunction showed by our case is not a classic feature of SoS and remains unexplained. It could be postulated that the increased pro-thrombotic risk

and the liver dysfunction are uncommon features of SoS (particularly in cases presenting with CHI) or, alternatively, another as yet undiagnosed condition could be responsible for the remaining atypical features of our patient.

Our case is in line with other reports documenting an association of CHI and SoS. It also shows that CHI can persist and require medical treatment with diazoxide beyond the neonatal period. However, low diazoxide doses can be sufficient to revert the hyperinsulinaemic status and guarantee normogycaemia. We also hypothesized that liver dysfunction and extensive thrombosis might be part of an extended SoS phenotype, particularly in patients presenting with CHI. Finally, our case shows that an early neonatal diagnosis of rare genetic conditions is challenging, especially in acutely unwell patients, and that in complex cases with incomplete, atypical or overlapping phenotypes, broad genomic testing by whole exome or whole genome sequencing may be a useful diagnostic strategy.

**Acknowledgements:** We thank the Rapid Paediatric Sequencing Project (RaPs) research team at Great Ormond Street Hospital (GOSH) for performing the rapid whole genome sequencing (WGS) and allowing the underlying diagnosis of Sotos syndrome to be made in our patient.

**Conflict of interest:** The authors disclose no conflict of interest.

**Patient Consent:** Subjects (or their parents or guardians) have given their written informed consent.

**REFERENCES**


1. Weksberg R, Shuman C, Bruce Beckwith J: Beckwith-Wiedemann syndrome. Am J Med Genet A. 2010;18:8-14.
2. Arnoux JB, Verkarre V, Sain-Martin C, Montravers F, Brassier A, Valayannopoulos V, Brunelle F, Fournet JC, Robert JJ, Aigrain Y, Bellane C, de Lonlay P: Congenital hyperinsulinism: Current trends in diagnosis and therapy. Orphanet J Rare Dis. 2011; 6:63.
3. Nakamura Y, Takagi M, Yoshihashi M, Miura M, Narumi S, Hasegawa T, Miyake Y, Hasegawa Y: A case with neonatal hyperinsulinameic hypoglycaemia: It is a characteristic complication of sotos syndrome. Am J Med Genet A. 2015;167A:1171-1174.
4. Matsuo T, Ihara K, Ochiai M, Kinjo T, Yoshikawa Y, Kojima-Ishii K, Noda M, Mizumoto H, Misaki M, Minagawa K, Tominaga K, Hara T: Hyperinsulinaemic hypoglycaemia of infancy in Sotos syndrome. Am J Med Genet A. 2013;161A:34-37.
5. González Casado I, De la PuenteArévalo A, Lopez Moreira O, Lapunzina P, Gracia Bouthelier R: An Pediatr. 2012;76:232-234.
6. Tatton-Brown K, Cole TRP, Rahman N: Sotos Syndrome [Updated 2015 Nov 19]. GeneReviews® [online]. University of Washington: Seattle; 2004. p. 1993-2017.
7. Cole TR, Hughes HE: Sotos syndrome. J Med Genet. 1990;27:571-576.
8. Cole TR, Hughes HE: Sotos syndrome: a study of the diagnostic criteria and natural history. J Med Genet. 1994;31:20-32.
9. Hook EB, Reynolds JW: Cerebral gigantism: endocrinological and clinical observations of six patients including a congenital giant, concordant monozygotic twins, and a child who achieved adult gigantic size. J Pediatr. 1967;70:900-914.

10. Giurgea I, Bellanné-Chantelot C, Ribeiro M, Hubert L, Sempoux C, Rober JJ, Blankenstein O, Hussain K, Brunelle F, Nihou-Fékété C, Rahier J, Jauber F, de Lonlay P: Molecular Mechanisms of Neonatal Hyperinsulinism. Horm Res. 2006;66:289-296.
11. Toda N, Ihara K, Kojima-Ishii K, Ochiai M, Ohkubo K, Kawamoto Y, et al: Hyperinsulinemic hypoglycemia in Beckwith-Wiedemann, Sotos, and Kabuki syndromes: A nationwide study in Japan. Am J Med Genet A. 2017;173A:360-367.
12. Al-Otaibi H, Senniappan S, Alam S, Hussain K: Biochemical studies in patients with hyperinsulinaemic hypoglycaemia. Eur J Pediatr. 2013;172:1435-1440.
13. Shah P, Rahman SA, Demirbilek H, Güemes M, Hussain K: Hyperinsulinaemic hypoglycaemia in children and adults. Lancet Diabetes Endocrinol. 2016;5:729-742.
14. Stanley CA: Hypoglycaemia in the neonate. Pediatr Endocrinol Rev. 2006;4:76-81.
15. Kapoor RR, Flanagan SE, James C, Shield J, Ellard S, Hussain K. Hyperinsulinaemic hypoglycaemia: Arch Dis Child. 2009;94:450-457.
16. Veldman A, Nold MF, Michel-Behnke I: Thrombosis in the critically ill neonate: incidence, diagnosis, and management. Vasc Health Risk Manag. 2008;4:1337-1348.
17. Daphne Yau MS-E, Amish Chinoy, Philip G Murray, Indi Banerjee: Central Venous Cathether-Associated Thrombosis in Children with Congenital Hyperinsulinism. ESPE Abstracts. 2018; 89 FC93.
18. Meigs JB, Mittleman MA, Nathan DM, Tofler GH, Singer DE, Murphy-Sheehy PM, Lipinska I, D'Agostino RB, Wilson PW: Hyperinsulinemia, hyperglycemia, and impaired hemostasis: the Framingham Offspring Study. JAMA. 2000; 283:221-228.

19. Després JP, Lamarche B, Mauriège P, Cantin B, Dagenais GR, Moorjani S, Lupien PJ: Hyperinsulinemia as an independent risk factor for ischemic heart disease. N Engl J Med. 1996;334:952-957.

**LEGEND**

**Figure 1.**

Baby at 3 weeks of age showing contractures of fingers and facial features. The downslanting palpebral fissures and pointed chin are in keeping with SoS.

**Figure 2.**

The growth chart shows the progressive increase in the disproportion between the patient's length and weight (length>weight). It also shows the unusually relatively normal head circumference for a patient with Sotos syndrome.