CASE REPORT

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Hyperinsulinemia in Sotos Syndrome with a *de novo NSD1* Deletion

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What is already known on this topic?

Sotos syndrome belongs to a group of congenital overgrowth disorders. Most of the cases with Sotos syndrome are due to intragenic mutations and deletions of the NSD1 which is located at chromosome 5q35. To date, over 600 disease-associated variants in NSD1 have been reported to the Human Gene Mutation Database. Most of the variants are missense mutations, followed by small deletions and gross deletions. Congenital hyperinsulinemic hypoglycaemia (CHI) has been described as an uncommon feature of Sotos syndrome, initially reported as transient CHI in 1990. A few cases of Sotos patients with transient CHI and point mutations in the *NSD1* gene were described. NSD1 is not known to be directly involved in regulating insulin secretion but patients with Sotos syndrome have alterations in the IGF-1 axis which could play a role in β-cell hyperplasia.

What this study adds?

Our case reports a patient with Sotos syndrome and prolong CHI due to de novo, novel large genomic deletion encompassing 24 OMIM genes including the entire *NSD1* gene that has never been presented before. In this case CHI that persisted for almost two years. After treatment with diazoxide was started, the patient responded with a serious side effect, leading to heart failure. A treatment changed to Octreotide with no response. Diazoxide was then resumed at a low dose, less than 5 mg/kg/day, because of the risk of cardiac complications. Doses were required for nearly 2 years and were sufficient to avoid hyperinsulinemia and to ensure normoglycemia. Our proposal is that, in neonatal diagnostics, the phenotypic spectrum of Sotos syndrome should include HI as a significant feature.

ABSTRACT

Sotos syndrome belongs to the group of diseases characterised by features such as facial dysmorphism, intellectual disability, hypotonia and overgrowth. Usually, Sotos syndrome is caused by heterozygous mutations in the *NSD1* gene at chromosome 5q35 or by large genomic deletions of the same region. Genotype-phenotype correlations have mainly been reported as an association of significant or major abnormalities and presence of 5q35 deletions rather than intragenic deletions or point mutations in *NSD1*. Congenital hyperinsulinemic hypoglycaemia (CHI) has been described as an uncommon feature in the presentation of Sotos syndrome. Most of the patients with Sotos syndrome and transient CHI were carriers of 5q35 deletions, while persistent CHI has been recently reported in individuals with point mutations or small *NSD1* deletions. We report the clinical features and medical treatment in a new-born child with Sotos syndrome and CHI that was present for almost two years. Genetic cause of Sotos syndrome in this case was a novel, large genomic deletion encompassing 24 Online Mendelian Inheritance in Man genes including the entire *NSD1* gene and six other potentially morbid genes. Our report describes challenges in diagnosis and management of this rare genetic condition. We propose, that in neonatal diagnostics, the phenotypic spectrum of Sotos syndrome should include CHI as a characteristic feature and molecular genetic testing should be done by whole genome analysis.

Keywords: Hyperinsulinemia, hypoglycaemia, *NSD1*, overgrowth, Sotos syndrome

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Introduction

Sotos syndrome (SOS) [Online Mendelian Inheritance in Man (OMIM) #117550] belongs to a group of congenital overgrowth disorders characterised by facial dysmorphism, brain involvement, prenatal and postnatal overgrowth, cardiac defects, kidney problems, scoliosis and loss of vision and hearing (1,2).

SOS is caused by haploinsufficiency of the *NSD1* gene at 5q35.2-q35.3 coding for nuclear receptor binding SET domain 1 protein. The NSD1 protein functions as a transcriptional regulator of chromatin through the histone methyltransferase activity (1,3). To date, 623 disease-associated variants in *NSD1* have been reported to the Human Gene Mutation Database (HGMD Professional) (https://my.qiagendigitalinsights.com/bbp/view/hgmd/pro/gene.php?gene=NSD1). Most of the variants are missense mutations (n=263), followed by small deletions (n=142) and gross deletions (n=63). Gross deletions may result in removal of a single or several exons or the entire *NSD1* gene with adjoining genes. Deletions have been reported to vary from 3.8 kb to 5 Mb, according to HGMD Professional. The majority of the large genomic deletions including *NSD1* appear *de novo* while familial cases with missense mutations in the *NSD1* gene have also been reported (1,4).

Molecular techniques, such as genome-wide genotyping or chromosomal microarray (CMA) and multiplex ligation-dependent probe amplification are usually used for detection of large genomic deletions encompassing *NSD1* or the *NSD1* intragenic deletions, that can also be confirmed by fluorescence *in situ* hybridization (FISH).

Congenital hyperinsulinemic hypoglycaemia (CHI) due to inappropriate insulin secretion leading to severe hypoglycemia may be an isolated finding or a feature of the syndrome. CHI has been described as an uncommon feature of SOS, and was initially reported as transient CHI in 1990 (1,5). Over the last decade, the number of reported cases of SOS with 5q35 deletions and transient CHI became more numerous (6,7,8). Most of the cases of SOS with CHI were caused by microdeletions but Sotos patients with transient CHI and point mutations in the *NSD1* gene have also been described (6,9). Thus, Grand et al. (6) presented seven patients, all carriers of *NSD1* point mutations, three of whom demonstrated persistent CHI while five of them had atypical features of SOS. These authors concluded that the CHI present in Sotos patients with *NSD1* point mutations could not be explained by the deletion of additional genes in the deleted 5q35 region.

A large difference in the frequency of 5q35 microdeletions causing SOS was observed in Japanese (49%) and non-Japanese (6%) patients (10,11). A partial or whole *NSD1* gene deletions were present in ~10% of 30 Brazilian Sotos patients of non-Japanese ancestry (12). In a cohort of Sotos patients from France and the UK, 5q35 the frequency of microdeletions was 18% and 5%, respectively, while intragenic *NSD1* mutations responsible for Sotos phenotype were detected in 49% of French and in more than 70% of British patients (13,14).

In this report, we present clinical features, molecular diagnostics and medical treatment of persistent CHI in a patient with SOS caused by a *de novo* large genomic deletion encompassing 24 OMIM genes including the entire *NSD1* gene.

In this report, we describe the clinical features and medical management of a newborn with SOS complicated by congenital hyperinsulinism, a condition that persisted for nearly two years. We also highlight the diagnostic challenges and therapeutic considerations associated with this rare genetic presentation.

According to national regulations, presentation of this case report did not require approval from an ethics committee. Informed consent for publication was obtained from the patient's parents.

Case Presentation

A full-term male baby [gestational age of 39 weeks, birth weight 3855 g (+1 standard deviation score, SDS), birth length 53 cm (+1SDS), head circumference 37 cm (+1SDS)], the second child of non-consanguineous Caucasian parents, was born by emergency Cesarean section because of a pathological cardiotocography trace. Antenatal scans showed polyhydramnios, abnormal flow in the umbilical cord and in the arteria cerebri media, as well an abnormal brain morphology. Apgar score was 1-5-10 min: 3-7-8p. Directly after delivery, the patient was found to be hypotonic and hypoglycaemic (P-glucose 0.6 mmol/L) and was admitted to the neonatal intensive care unit. He required intravenous (IV) high concentration glucose infusions with a utilization rate of 13-14 mg/kg/min and, due to tachypnea, he was treated with positive pressure therapy, using continuous positive pressure therapy.

Physical Characteristics

Clinical examination revealed syndromic features, including macrocephaly with prominent forehead, hypertelorism, posteriorly rotated low set ears, short philtrum, flat nasal bridge, and general hypotonia. SOS was suspected.

Systemic Event

At six days of age, he developed repeated seizures, not linked to hypoglycaemia, confirmed with video electroencephalography. Treatment with antiepileptics, phenobarbitone and phenytoin was started. Neuroimaging of brain showed hypo-myelinization, ischemia, a periventricular white matter lesion and reduction of

the corpus callosum. A cardiac ultrasound showed a muscular ventricular-septal defect.

Glycemic Event and Treatment

Recurrent hypoglycaemia required continuous glucose infusion and nutritional intake by breastfeeding and nasogastric tube feeding. Repeated diagnostic fast tolerance test was done at the age of 15 days. A critical sample was obtained that revealed plasma-glucose 2.6 mmol/L, C-peptide 0.36 nmol/L, and p-insulin 2.1 mIU/mL. Metabolic investigation for carnitine, methylmalonate, methionine and free amino acids was normal. Plasma beta- hydroxybutyrate was not analyzed and an ammonium level was 67 umol/L, however this was taken at another occasion. The clinical presentation did not resemble hypopituitarism and this diagnosis was excluded because of clinical and laboratory findings.

Diazoxide, as a first-line treatment for CHI, was initiated at a dose 10 mg/kg/day on day 15 with normalisation of p-glucose at day 18. However, due to fluid retention and development of severe pulmonary hypertension with lung oedema and heart failure, diazoxide was discontinued on day 19. The condition of the patient was critical, requiring intubation and respiratory treatment and was regarded as diazoxide "toxicity" affecting the heart. At the intensive care unit, normoglycemia 4-7 mmol/L was observed until patient's age of 29 days, when he was discharged to the pediatrics care unit.

At day 30, a persistent hypoglycaemia re-occurred and so IV glucose with a utilization rate to 6 mg/kg/min was started. Due to the suspicion of possible diazoxide heart toxicity, octreotide treatment was initiated on day 35, at a dose of 3.5 µg/kg/day and increased by 2 µg/kg/day up to 20 µg/kg/day over 10 days. However, episodes of hypoglycemia persisted. Octreotide treatment was considered ineffective and was discontinued at day 45. On some occasions, diazoxide was carefully re-initiated at low doses of 1 and later 2 mg/kg/day. These doses were well tolerated and therefore were increased to 5 mg/kg/day for maintained normoglycemia. The baby was fed every 2.5 hours and was able to fast for five hours. He maintained normoglycemia at day 46 when glucose infusion was discontinued. Patient's treatments during the first two months of life are presented in Figure 1.

Follow-up

The patient was discharged from hospital at 12 weeks of age with diazoxide treatment at dose of 5 mg/kg/day. He was mainly fed by nasogastric tube, which was discontinued at six months of age. He was growing at 0SDS for both height and weight, based on Swedish reference and genetic potential was a target height of 0SDS. His head circumference was +3SDS according to the expectations for those with SOS. He was diagnosed with mild mental retardation. At 15 months of age, the patient showed positive progress in motor development. He still required a small dose of diazoxide of 1.5 mg/kg/day and at 18 months diazoxide at the same dose was needed only during infections. At two years of age hypoglycemic episodes completely resolved. Currently he is on a normal diet and can tolerate overnight fast without hypoglycaemia. His heart function was stable at follow-

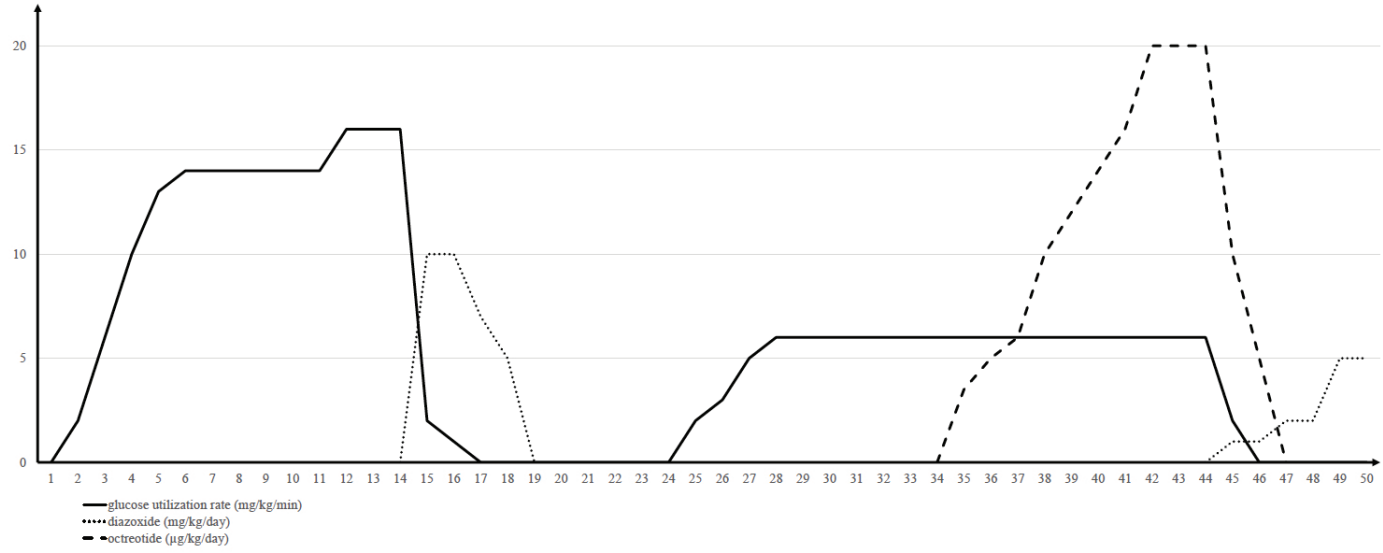

Figure 1. Glucose utilization, use of medication during treatment NICU. Blackline-glucose utilization rate (mg/kg/min), dotted line-diazoxide doses (mg/kg/day), dashed line-octreotide doses (µg/kg/day)
NICU: neonatal intensive care unit

up appointments. The patient was diagnosed with bronchial asthma and treated with conventional inhalation steroid. He has frequently been affected by viral infections complicated by mucus plugs in airways due to hypotonus and has often required short-term hospitalizations. The patient needs a team of specialists for his associated anomalies and development delay.

Materials and Methods

Clinical features, biochemical data, and medical treatments were collected from the patient's medical records and from personal observations of clinical follow up. Height, weight and head circumference were measured at each visit, and SDS were calculated using current Swedish National references (15,16).

Genetic Findings

The patient's DNA analyzed by CMA and revealed a 1349-1354 kb deletion on chromosome 5: arr[GRCh38] 5q35.2q35.3(176,597,879-177,949,621)x1 (Figure 2). The deleted region overlapped 36 HGNC and 24 OMIM genes: *GPRIN1, SNCB, UNC5A, HK3, UIMC1, ZNF346,* fibroblast growth factor receptor 4 *(FGFR4) gene, NSD1, RAB24, MXD3, PRELID1, LMAN2, RGS14, SLC34A1, PFN3, F12, GRK6, DBN1, PDLIM7, DOK3, DDX41, FAM193B, PRR7* and *B4GALT7* (Table 1).

The deletion of the *NSD1* gene that would result in haploinsufficiency represents the major cause of SOS. Therefore, this loss was interpreted as a pathogenic copy number variant (CNV), causing the syndrome in our patient. The deletion was confirmed by FISH with a locus specific *NSD1* probe (Figure 3). The specific signal for *NSD1* signal was seen on only one homologous chromosome 5. Subsequent FISH analysis of parental samples did show normal signal pattern with presence of the *NSD1* signals on both chromosomes. Thus, we concluded that the deletion in this case appeared to be *de novo*.

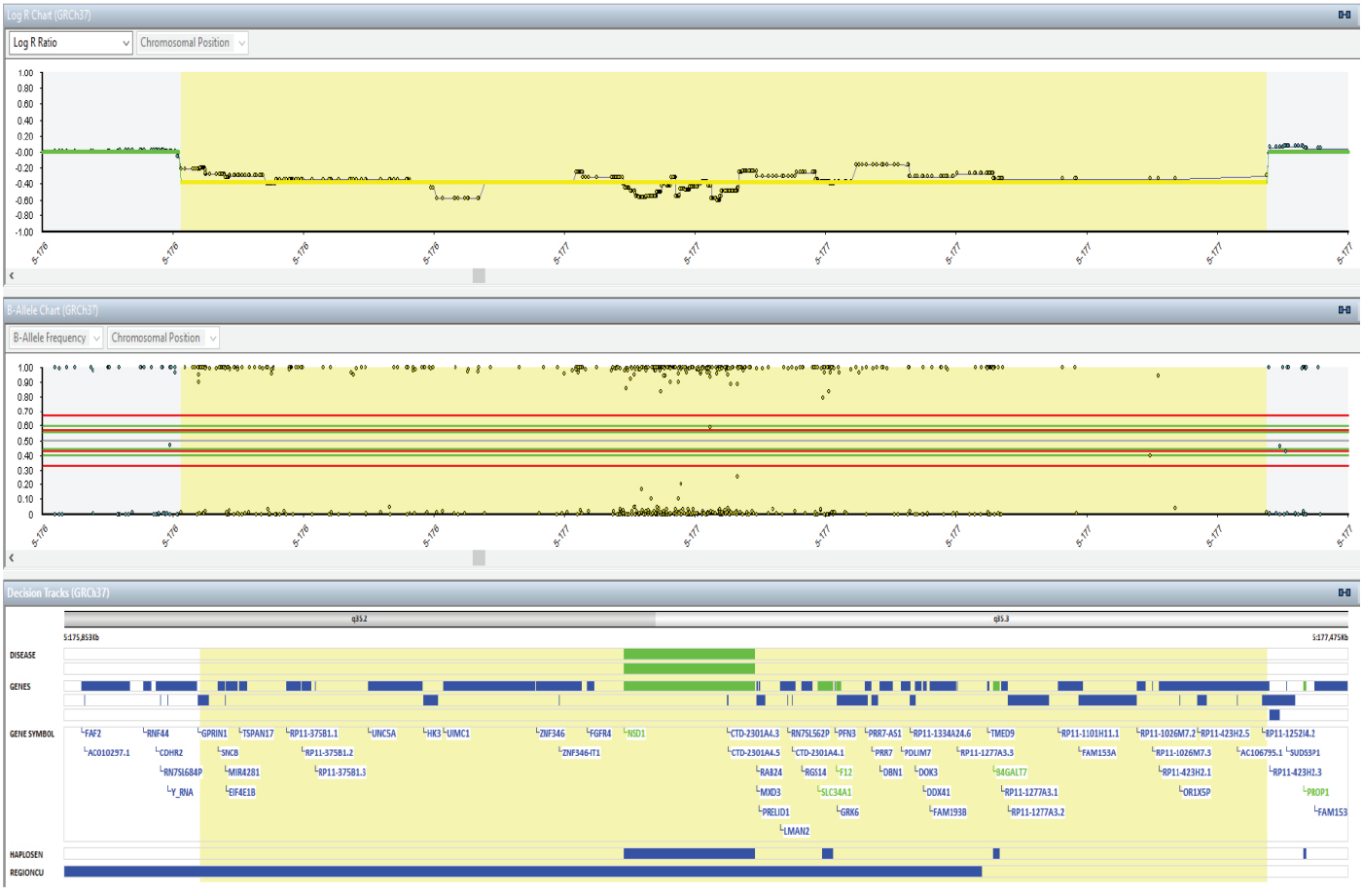

Figure 2. Deletion on chromosome 5q35.2q35.3 [arr(GRCh38) 5q35.2q35.3(176,597,879-177,949,621)x1] detected by genome wide genotyping and CNV analysis. Details of SNP array analysis are presented in Materials and Methods. The data are visualized in BlueFuse Multi software as Log2Ratio (upper panel), B-allele frequency (middle panel) and Decision Tracks. The deletion covers 24 genes, *NSD1* is shown in green. Boundaries of the deletion are shown as a yellow box. The list of all genes is available in Table 1

CNV: copy number variant, SNP: single nucleotide polymorphism

Table 1. The genes located at 5q35.2-q35.2 deleted in the patient

Gene		Start	End	OMIM	Morbid
B4GALT7	Beta-1,4-galactosyltransferase 7	177600132	177610330	604327	Ehlers-Danlos syndrome, spondylodysplastic type, 1 (AR)
DBN1	Drebrin 1	177456608	177474401	126660	-
DDX41	DEAD-box helicase 41	177511577	177516961	608170	-
DOK3	Docking protein 3	177501904	177511274	611435	-
EIF4E1B	Eukaryotic translation initiation factor 4E family member 1B	176630618	176646644	-	-
F12	Coagulation factor XII	177402133	177416583	610619	Angioedema, hereditary, 3 (AD) Factor XII deficiency (AR)
FAM153A	Family with sequence similarity 153 member A	177707981	177784435	-	-
FAM193B	Family with sequence similarity 193 member B	177519789	177554586	615813	-
FAM193B-DT	FAM193B divergent transcript	177554824	177555364	-	-
FGFR4	Fibroblast growth factor receptor 4	177086905	177098144	134935	Cancer progression/ metastasis (Unknown inheritance)
GPRIN1	G protein regulated inducer of neurite outgrowth 1	176595802	176610156	611239	-
GRK6	G protein-coupled receptor kinase 6	177403204	177442901	600869	-
HK3	Hexokinase 3	176880869	176899346	142570	-
LINC01574	Long intergenic non-protein coding RNA 1574	176743205	176743871	-	-
LMAN2	Lectin, mannose binding 2	177315805	177351840	609551	-
MIR4281	microRNA 4281	176629439	176629500	-	-
MXD3	MAX dimerization protein 3	177301461	177312757	609450	-
NSD1	Nuclear receptor binding SET domain protein 1	177131830	177300213	606681	Sotos syndrome (AD)
OR1X5P	Olfactory receptor family 1 subfamily X member 5 pseudogene	177836434	177837646	-	-
PDLIM7	PDZ and LIM domain 7	177483394	177497606	605903	-
PDLIM7-AS1	PDLIM7 antisense RNA 1	177494995	177503647	-	-
PFN3	Profilin 3	177400109-	177400661	612812	-
PRELID1	PRELI domain containing 1	177303799	177306949	605733	-
PRMT1P1	Protein arginine methyltransferase 1 pseudogene 1	177265580	177266588	-	-
PRR7	Proline rich 7, synaptic	177446445	177456286	618306	-
PRR7-AS1	PRR7 antisense RNA 1	177438503	177447982	-	-
RAB24	RAB24, member RAS oncogene family	177301198	177303744	612415	-
RGS14	Regulator of G protein signaling 14	177357924	177372596	602513	-
SLC34A1	Solute carrier family 34 member 1	177379235	177398848	182309	Fanconi renotubular syndrome 2 (AR) Hypercalcemia, infantile, 2 (AR) Nephrolithiasis/osteoporosis, hypophosphatemic, 1 (AD)
SNCB	Synuclein beta	176620082	176630556	602569	Dementia, Lewy body; DLB (AD)
TMED9	Transmembrane p24 trafficking protein 9	177592203	177597242	-	-
TSPAN17	Tetraspanin 17	176647387	176659054	-	-
UIMC1	Ubiquitin interaction motif containing 1	176905005	177022633	609433	-
UNC5A	Unc-5 netrin receptor A	176810519	176880898	607869	-
ZNF346	Zinc finger protein 346	177022696	177081189	605308	-
ZNF346-IT1	ZNF346 intronic transcript 1	177051714	177052963	-	-

Genomic positions according GRChr38/hg38.
AR: autosomal recessive, AD: autosomal dominant, OMIM: Online Mendelian Inheritance in Man

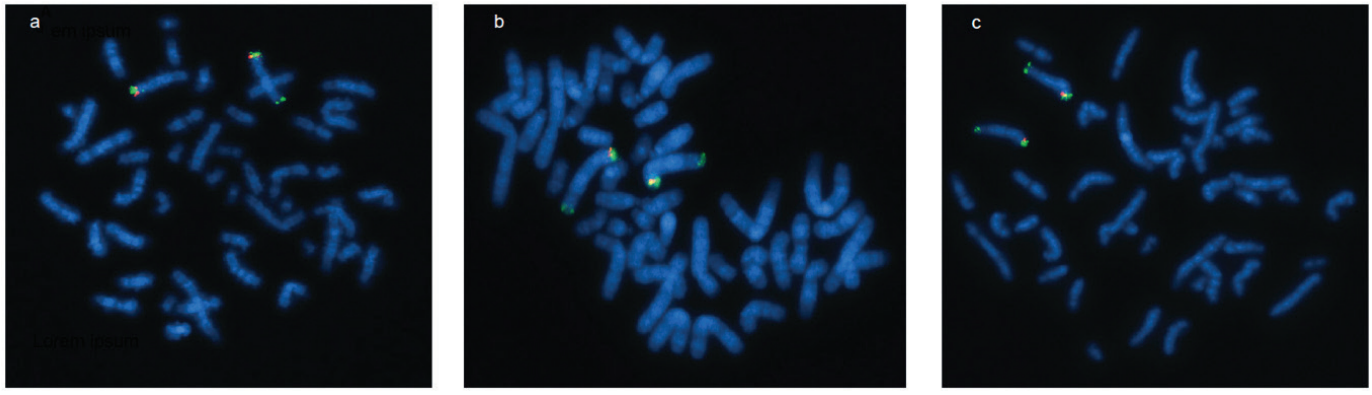

Figure 3. Fluorescence *in situ* hybridization results with *NSD1* specific probe (5q35) (Cytovision Technologies). a) *NSD1* deletion is seen in metaphase derived from the patient's peripheral blood. FISH on parental blood samples show presence of two signals on both chromosomes [b) paternal sample, c) maternal sample]

Molecular genetic analyses targeted next generation seuencing with a congenital hyperinsulinism sequencing panel with CNV detection did not identify any pathogenic variants. Minimum NGS coverage ≥20X for all exons and ±10bp of flanking DNA, and ≥10x from 11-20bp of flanking DNA. Average NGS coverage was 165x and fraction of bases covered with NGS was 99.5%. The following genes, *ABCC8, GCK, GLUD1, HADH, HNF1A, HNF4A, SLC16A1,* and *UCP2* were analyzed.

High resolution CMA was performed on peripheral blood collected in EDTA tubes using standard procedure, and DNA was isolated from 200 µL of whole blood using the QiaSymphony (Qiagen, Valencia, CA, USA) according to the manufacturer's instructions. DNA was quantified using the Nanodrop 1000 Spectrophotometer (Thermo Scientific, Waltham, MA, USA).

CMA or genome-wide genotyping used for detection of CNVs was performed with the Infinium CytoSNP-850K v1.2 Beadchip (Illumina, San Diego, CA, USA) containing approximately 850,000 single nucleotide polymorphisms markers over the entire genome with an average probe spacing of 1.8kb. Two hundred nanogrammes of ng DNA was hybridized on a beadchip after whole-genome amplification, followed by scanning on the HiScan machine (Illumina). Genotyping results were visualized, normalized and clustered using the Genotyping module of the GenomeStudio software (Illumina) and by BlueFuse Multi software (v.4.4). The cnvPartition 3.2.0 (Illumina) was applied for CNV detection by retrieving Log R Ratio (LRR, the ratio between the observed and the expected probe intensity) and the B allele frequency (BAF). When a CNV is absent, the LRR is around zero, and the BAF is 0, 0.5, or 1 depending on genotypes AA, AB, and BB. Deviations from the expected values indicate copy number alterations. Human genome GRCh38 (NCBI)/hg38 (UCSC) was used for assigning all chromosomal positions. CNVs overlapping with a region of known microdeletion or microduplication syndromes and/or disease-causing genes were classified as pathogenic. The Database of Genomic Variants, the OMIM, and the dbVar Genome Browser and Database of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources were used to access known microdeletion and microduplication syndromes.

FISH analysis specific for chromosome 5 was performed on metaphase slides according to the manufacturer's standard protocol (Cytocell Technologies, Cambridge, UK). Probes detecting Cri-du-Chat syndrome on 5p15.2 (*CTNND2* in red) and 5p15.31 (*UBE2QL1* in green) were used as control probes. The third probe in this mix was a *NSD1* specific probe on 5q35 labelled in green. The slides were dehydrated and co-denatured with the probes at 73 °C for 5 min. Hybridization was done overnight at 37 °C using Hybrite™ (Vysis, Downers Grove, IL, USA). The slides were counterstained with 4',6-diamidino-2-phenylindole (Vysis). The images were captured by Leica Microscope and analyzed using Cytovision Image Analysis and Capture System (version 7.5) (Leica Biosystems, Maarn, NL).

Discussion and Conclusion

We present a patient with characteristic features of SOS, persistent CHI and a *de novo* genomic deletion encompassing 24 OMIM genes including the entire *NSD1* gene. Among the 24 OMIM genes, seven were classified as morbidity-associated (Table 1). Notably, one of the deleted genes, *HK3*-hexokinase, a member of the hexokinase family, is involved in the first step of glucose metabolism (17). However, neither sequence variants in *HK3* gene or haploinsufficiency have been linked with hyperinsulinism. *HK3* sequence variants have been suggested to be associated with ovarian failure and affect the glycolysis important in the development and progression of different neoplasms (18,19,20). Another interesting gene is the *FGFR4*. Sequence variants in *FGFR4* gene or haploinsufficiency have

been suggested to be associated with diverse phenotypes but not with CHI (12,21).

A heterozygous mutation in the *NSD1* gene (MIM 606681) identified in more than 75% of cases is a common genetic cause of SOS (22). Previously, CHI was reported as an unusual presentation in Sotos patients (5,23,24), but in recent years the number of studies reporting CHI in this condition has increased (7,8). The concurrent presence of *NSD1* defects and CHI in SOS has also been reported. Transient neonatal CHI was described in Japanese patients with SOS where 7 of 8 patients harboured a 5q35 microdeletion but only 3 of 8 required diazoxide treatment (7,8). In a national Japanese survey, CHI was present in about 10% of children with SOS, indicating strong association between these two features (25). Furthermore, CHI was reported in seven patients with SOS caused by point mutations in *NSD1* (26). In 3 of 7 patients, CHI persisted for more than one year. These results challenge the previous hypothesis that CHI in SOS is due to the deletion of additional genes in the 5q35 region. Moreover, *NSD1* is proposed to play a role in glucose homeostasis. *NSD1* was known as a histone methyltransferase and is implicated in the regulation of chromatin and gene expression (6). However, *NSD1* is expressed in human pancreatic beta cells, as demonstrated by bulk islet cell analyses and single-cell RNA-sequencing (6,27,28). Association between SOS, response to diazoxide treatment and CHI disappearance over time was also described by Kapoor et al. (29), although the exact mechanisms are still not completely understood.

The present case exhibited resolution of his CHI, but it had persisted for almost two years; this is in line with previous publications that reported a similar association between SOS and CHI. The definition of transient hyperinsulinemic hypoglycaemia was poorly defined in earlier studies, and is characterized by spontaneous resolution within a few days but as late as six months of life (29). According to this definition, the transient CHI was prolonged in our case. It is unclear if this is due to the relatively large deletion. The patient required extra feeding and for almost two years was on medication with diazoxide, a ATP-sensitive potassium channel opener, the first-line therapy for CHI (30). It is important to note that our patient responded poorly to diazoxide, which led to heart failure. This meant that when diazoxide was reinitiated, it was at a low dose of less than 5 mg/kg/d because of the risk of heart complications. Nevertheless, the doses were sufficient to avoid hyperinsulinemia and to ensure normoglycaemia. Compared to our patient who required treatment with diazoxide for almost 2 years, previous reports have found diazoxide treatment was required for shorter periods, although this was up to 8 months of age in one report (31) and three children with point mutations in *NSD1* were treated over one year (6).

As practice shows, neonatal CHI needs the correct diagnosis and an adequate treatment to avoid neurological consequences. The presented patient with SOS also exhibited a broad spectrum of clinical features, especially in terms of CHI.

The identification of *NSD1* abnormalities in most patients with SOS makes a molecular diagnosis possible and helps to confirm a clinical diagnosis of SOS. Despite hypoglycemia being described as a minor feature in SOS, several reports on a genotype-phenotype correlation were published that warrant further research. We propose that, in neonatal diagnostics, the phenotypic spectrum of SOS should include HI as a significant feature.

This case demonstrates that early clinical diagnosis of this rare condition may be challenging and depends on subjective clinical experience and judgement. Experiences and lessons from our management may merit inclusion within medical discourse, and it is hoped this case report will serve as a reference for the diagnosis and treatment of similar patients in the future.

Ethics

Informed Consent: Informed consent for publication was obtained from the patient's parents.

Acknowledgments

We express our sincere gratitude to the patient and his family for their participation. We also thank Camilla Ernstsson, pediatric endocrine nurse, as well as the laboratory biomedical scientists at the Department of Clinical Genetics, for their valuable assistance.

Data Availability Statement

The dataset generated by genome wide genotyping using SNP-array (Illumina) is available upon request.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Elena Lundberg, Concept: Elena Lundberg, Magnus Burstedt, Irina Golovleva, Design: Elena Lundberg, Irina Golovleva, Data Collection or Processing: Elena Lundberg, Genetic analysis Magnus Burstedt, Irina Golovleva, Analysis or Interpretation: Elena Lundberg, Magnus Burstedt, Irina Golovleva, Writing: Elena Lundberg, Magnus Burstedt, Irina Golovleva.

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References

1. Tatton-Brown K, Douglas J, Coleman K, Baujat G, Cole TR, Das S, Horn D, Hughes HE, Temple IK, Faravelli F, Waggoner D, Turkmen S, Cormier-Daire V, Irrthum A, Rahman N; Childhood Overgrowth Collaboration. Genotype-phenotype associations in Sotos syndrome: an analysis of 266 individuals with NSD1 aberrations. Am J Hum Genet. 2005;77:193-204. Epub 2005 Jun 7
2. Leventopoulos G, Kitsiou-Tzeli S, Kritikos K, Psoni S, Mavrou A, Kanavakis E, Fryssira H. A clinical study of Sotos syndrome patients with review of the literature. Pediatr Neurol. 2009;40:357-364.

3. Aasland R, Stewart AF. The chromo shadow domain, a second chromo domain in heterochromatin-binding protein 1, HP1. Nucleic Acids Res. 1995;23:3168-3173.

4. van Haelst MM, Hoogeboom JJ, Baujat G, Brüggenwirth HT, Van de Laar I, Coleman K, Rahman N, Niermeijer MF, Drop SL, Scambler PJ. Familial gigantism caused by an NSD1 mutation. Am J Med Genet A. 2005;139:40-44.

5. Cole TR, Hughes HE. Sotos syndrome. J Med Genet. 1990;27:571-576.

6. Grand K, Gonzalez-Gandolfi C, Ackermann AM, Aljeaid D, Bedoukian E, Bird LM, De Leon DD, Diaz J, Hopkin RJ, Kadakia SP, Keena B, Klein KO, Krantz I, Leon E, Lord K, McDougall C, Medne L, Skraban CM, Stanley CA, Tarpinian J, Zackai E, Deardorff MA, Kalish JM. Hyperinsulinemic hypoglycemia in seven patients with de novo NSD1 mutations. Am J Med Genet A. 2019;179:542-551. Epub 2019 Feb 4

7. 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. Hyperinsulinemic hypoglycemia of infancy in Sotos syndrome. Am J Med Genet A. 2013;161A:34-37. Epub 2012 Dec 13

8. Nakamura Y, Takagi M, Yoshihashi H, Miura M, Narumi S, Hasegawa T, Miyake Y, Hasegawa Y. A case with neonatal hyperinsulinemic hypoglycemia: It is a characteristic complication of Sotos syndrome. Am J Med Genet A. 2015;167A:1171-1174. Epub 2015 Feb 25

9. Carrasco Salas P, Palma Milla C, Lezana Rosales JM, Benito C, Franco Freire S, López Siles J. Hyperinsulinemic hypoglycemia in a patient with an intragenic NSD1 mutation. Am J Med Genet A. 2016;170A:544-546. Epub 2015 Oct 21

10. Kurotaki N, Harada N, Shimokawa O, Miyake N, Kawame H, Uetake K, Makita Y, Kondoh T, Ogata T, Hasegawa T, Nagai T, Ozaki T, Touyama M, Shenhav R, Ohashi H, Medne L, Shiihara T, Ohtsu S, Kato Z, Okamoto N, Nishimoto J, Lev D, Miyoshi Y, Ishikiriyama S, Sonoda T, Sakazume S, Fukushima Y, Kurosawa K, Cheng JF, Yoshiura K, Ohta T, Kishino T, Niikawa N, Matsumoto N. Fifty microdeletions among 112 cases of Sotos syndrome: low copy repeats possibly mediate the common deletion. Hum Mutat. 2003;22:378-387.

11. Kurotaki N, Imaizumi K, Harada N, Masuno M, Kondoh T, Nagai T, Ohashi H, Naritomi K, Tsukahara M, Makita Y, Sugimoto T, Sonoda T, Hasegawa T, Chinen Y, Tomita Ha HA, Kinoshita A, Mizuguchi T, Yoshiura Ki K, Ohta T, Kishino T, Fukushima Y, Niikawa N, Matsumoto N. Haploinsufficiency of NSD1 causes Sotos syndrome. Nat Genet. 2002;30:365-366. Epub 2002 Mar 18

12. Fagali C, Kok F, Nicola P, Kim C, Bertola D, Albano L, Koiffmann CP. MLPA analysis in 30 Sotos syndrome patients revealed one total NSD1 deletion and two partial deletions not previously reported. Eur J Med Genet. 2009;52:333-336. Epub 2009 Jul 9

13. Rio M, Clech L, Amiel J, Faivre L, Lyonnet S, Le Merrer M, Odent S, Lacombe D, Edery P, Brauner R, Raoul O, Gosset P, Prieur M, Vekemans M, Munnich A, Colleaux L, Cormier-Daire V. Spectrum of NSD1 mutations in Sotos and Weaver syndromes. J Med Genet. 2003;40:436-440.

14. Douglas J, Hanks S, Temple IK, Davies S, Murray A, Upadhyaya M, Tomkins S, Hughes HE, Cole TR, Rahman N. NSD1 mutations are the major cause of Sotos syndrome and occur in some cases of Weaver syndrome but are rare in other overgrowth phenotypes. Am J Hum Genet. 2003;72:132-143. Epub 2002 Dec 2

15. Niklasson A, Albertsson-Wikland K. Continuous growth reference from 24th week of gestation to 24 months by gender. BMC Pediatr. 2008;8:8.

16. Wikland KA, Luo ZC, Niklasson A, Karlberg J. Swedish population-based longitudinal reference values from birth to 18 years of age for height, weight and head circumference. Acta Paediatr. 2002;91:739-754.

17. Xu W, Liu WR, Xu Y, Tian X, Anwaier A, Su JQ, Zhu WK, Shi GH, Wei GM, Huang YP, Qu YY, Zhang HL, Ye DW. Hexokinase 3 dysfunction promotes tumorigenesis and immune escape by upregulating monocyte/macrophage infiltration into the clear cell renal cell carcinoma microenvironment. Int J Biol Sci. 2021;17:2205-2222.

18. Krasnov GS, Dmitriev AA, Sadtritdinova AF, Fedorova MS, Snezhkina AV, Melnikova NV, Poteryakhina AV, Nyushko KM, Belyakov MM, Kaprin AD, Zaretsky AR, Kudryavtseva AV. [Evaluation of gene expression of hexokinases in colorectal cancer with the use of bioinformatics methods]. Biofizika. 2015;60:1050-1056. [In Russian]

19. Qin Y, Sun M, You L, Wei D, Sun J, Liang X, Zhang B, Jiang H, Xu J, Chen ZJ. ESR1, HK3 and BRSK1 gene variants are associated with both age at natural menopause and premature ovarian failure. Orphanet J Rare Dis. 2012;7:5.

20. He C, Kraft P, Chen C, Buring JE, Paré G, Hankinson SE, Chanock SJ, Ridker PM, Hunter DJ, Chasman DI. Genome-wide association studies identify loci associated with age at menarche and age at natural menopause. Nat Genet. 2009;41:724-728. Epub 2009 May 17

21. Shah RN, Ibbitt JC, Alitalo K, Hurst HC. FGFR4 overexpression in pancreatic cancer is mediated by an intronic enhancer activated by HNF1alpha. Oncogene. 2002;21:8251-8261.

22. Tatton-Brown K, Rahman N. Clinical features of NSD1-positive Sotos syndrome. Clin Dysmorphol. 2004;13:199-204.

23. Cole TR, Hughes HE. Sotos syndrome: a study of the diagnostic criteria and natural history. J Med Genet. 1994;31:20-32.

24. Kapoor RR, Flanagan SE, Arya VB, Shield JP, Ellard S, Hussain K. Clinical and molecular characterisation of 300 patients with congenital hyperinsulinism. Eur J Endocrinol. 2013;168:557-564.

25. Giurgea I, Bellanné-Chantelot C, Ribeiro M, Hubert L, Sempoux C, Robert JJ, Blankenstein O, Hussain K, Brunelle F, Nihoul-Fékété C, Rahier J, Jaubert F, de Lonlay P. Molecular mechanisms of neonatal hyperinsulinism. Horm Res. 2006;66:289-296. Epub 2006 Sep 26

26. Toda N, Ihara K, Kojima-Ishii K, Ochiai M, Ohkubo K, Kawamoto Y, Kohno Y, Kumasaka S, Kawase A, Ueno Y, Futatani T, Miyazawa T, Nagaoki Y, Nakata S, Misaki M, Arai H, Kawai M, Sato M, Yada Y, Takahashi N, Komatsu A, Maki K, Watabe S, Sumida Y, Kuwashima M, Mizumoto H, Sato K, Hara T. Hyperinsulinemic hypoglycemia in Beckwith-Wiedemann, Sotos, and Kabuki syndromes: a nationwide survey in Japan. Am J Med Genet A. 2017;173:360-367. Epub 2016 Nov 7

27. Ackermann AM, Wang Z, Schug J, Naji A, Kaestner KH. Integration of ATAC-seq and RNA-seq identifies human alpha cell and beta cell signature genes. Mol Metab. 2016;5:233-244.

28. Wang YJ, Schug J, Won KJ, Liu C, Naji A, Avrahami D, Golson ML, Kaestner KH. Single-cell transcriptomics of the human endocrine pancreas. Diabetes. 2016;65:3028-3038. Epub 2016 Jun 30

29. Kapoor RR, James C, Hussain K. Hyperinsulinism in developmental syndromes. Endocr Dev. 2009;14:95-113. Epub 2009 Feb 27

30. Aynsley-Green A, Hussain K, Hall J, Saudubray JM, Nihoul-Fékété C, De Lonlay-Debeney P, Brunelle F, Otonkoski T, Thornton P, Lindley KJ. Practical management of hyperinsulinism in infancy. Arch Dis Child Fetal Neonatal Ed. 2000;82:F98-F107.

31. Cerbone M, Clement E, McClatchey M, Dobbin J, Gilbert C, Keane M, Boukhibar L, Williams H, Gagunashvili A, Dattani MT, Hurst J, Shah P. Sotos syndrome presenting with neonatal hyperinsulinaemic hypoglycaemia, extensive thrombosis, and multisystem involvement. Horm Res Paediatr. 2019;92:64-70. Epub 2019 Mar 15