Case Report

Hyperinsulinemia in Sotos Syndrome with a de novo NSD1 Deletion

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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. The 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 of a new born child with transient CHI that was present for two years. Genetic cause of Sotos syndrome in this case was a novel, large genomic deletion encompassing 24 OMIM genes including the entire NSD1 gene and 6 other Morbid genes. Our report shows challenges in diagnostics 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 (OMIM #117550) (SOS) 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). Sotos syndrome is caused by haploinsufficiency of 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 can result in removal of one single or several exons or entire NSD1 with adjoining genes and the deletions’ size varies from 3.8 kb to 5 Mb according to HGMD Professional. Majority of the large genomic deletions containing 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 (MLPA) are usually applied for detection of large genomic deletions encompassing the NSD1 or the NSD1 intragenic deletions that can also be confirmed by fluorescence in situ hybridization (FISH). Congenital hyperinsulinic hypoglycaemia (CHI) due to an inappropriate insulin secretion leading to severe hypoglycaemia could be an isolated finding or a feature of the syndrome. CHI has been described as an uncommon feature of Sotos syndrome, initially reported as transient CHI in 1990 (1, 5). Over the last decade, a number of reported cases of Sotos syndrome with 5q35 deletions and transient CHI got larger (6-8). Most of the cases with Sotos syndrome and CHI were caused by microdeletions, however, Sotos patients with transient CHI and point mutations in the NSD1 gene have also been described (6, 9). Thus, Grand et al. presented seven patients, all carriers of NSD1 point mutations, three of which demonstrated persistent CHI and five of them had atypical features of Sotos syndrome (6). As the authors concluded, HI 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 Sotos syndrome 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 cohort of Sotos patients from France and UK 5q35 microdeletions frequency accounted for 18 and 5%, respectively while intragenic NSD1 mutations responsible for Sotos phenotype were found 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 Sotos syndrome caused by de novo large genomic deletion encompassing 24 OMIM genes including the entire NSD1 gene.

Case presentation

A full-term male baby (gestational age of 39 weeks, birth weight 3855 g (+1SDS), birth length 53 cm (+1SDS), head circumference 37 cm (+1SDS), second child of non-consanguineous Caucasian parents, was born by acute caesarean section in a view of pathologial cardiotocography trace. Antenatal scans showed polyhydramnios, abnormal flow in the umbilical cord and in the arteria cerebi 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 utilization rate (13-14 mg/kg/min) and due to tachypnea, he was treated with positive pressure therapy, CPAP.

Physical characteristics

Clinical examination revealed syndromic features such as macrocephaly with prominent forehead, hypertelorism, posteriorly rotated low sitting ears, short philtrum, flat nasal bridge, and general hypotonia. Sotos syndrome was suspected.

Systemic event

At 6 days of age, he developed repeated seizures, not linked to hypoglycaemia, confirmed with video electroencephalography EEG. Treatment with antiepileptics, phenobarbital and phenytoin was started. Neuroimaging of brain showed hypo-myelination, ischemia, a periventricular white matter lesion and reduction of the corpus callosum. A cardiac ultrasound showed a muscular ventricular-septum defect (VSD).

Glycaemic event and treatment

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

Diazoxide, as a first-line treatment for CHI, was initiated at 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” on 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 paediatrics care unit.

During the first two months of life, the patient was hospitalized in the intensive care unit, normoglycemia 4-7 mmol/L was observed until patient’s age of 29 days, when he was discharged to the paediatrics care unit. The patient was discharged from the Hospital at 12 weeks of age with diazoxide treatment at dose of 5 mg/kg/day. He obtained mainly nasogastric tube feeding, which was discontinued at 6 months of age. He was growing at 50th centile and height, according to Swedish reference and genetic potential, target height 107 cm. The child's head circumference was +2SDS according to the expectations for those with Sotos syndrome. 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 2 years of age hypoglycemia episodes completely resolved. Currently he is on a normal diet and can have overnight fast without hypoglycemia. Patient’s height normalisation was stable at follow-ups. The patient was diagnosed with asthma bronchial, treated with conventional method (inhalation steroid). He has frequently been affected by viral infections complicated with mucus plug in airways due to hypotonus and often required short-term hospitalisations. The patient needs a team of specialists for his associated anomalies and development delay.

**Genetic findings**

The patient’s DNA analysis with chromosomal microarray analysis (CMA) revealed 1349-1354 Kb deletion on chromosome 5: arr[GRCh38] 5q35.2;q53.3(176,597,879-177,949,621)x1 (Fig. 2). The deleted region overlapped 36 HGNC and 20 OMIM genes: GPRN1, SNCB, UNMC1, UMD3, PRAD11, LMAN2, RGS14, SLC34A1, PFN3, FY2, GCK, DBN1, PDLIM7, DOK3, DAX4, EAF19938, PRR7 and B4GALT7 (Table 1).

The gene that would result in haploinsufficiency represents the major cause of Sotos syndrome. Therefore, this aberration was interpreted as a pathogenic CNV, causing the disease in our patient. The deletion was confirmed by FISH with locus specific NSD1 probe (Fig. 3). A specific for NSD1 signal was seen only on one homologous chromosome 5. Following 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 de novo.

**Discussion and Conclusions**

Here, we present a patient with characteristic features of Sotos syndrome, persistent CHI and de novo genomic deletion encompassing 24 OMIM genes including the entire NSD1 gene. Among 24 OMIM genes seven were Morbid associated (Table 1). Notably, that one of the deleted genes, HK3- hexokinase is a member of hexokinase family, involved in the first step of glucose metabolism (15), however, neither sequence variants in HK3 gene nor haploinsufficiency have been linked with hyperinsulinism. Notably, that HK3 sequence variants have been suggested to be associated with ovarian failure and affect the glycolysis important in the development and progression of different neoplasia (16-18). Another interesting gene is Fibroblast Growth Factor Receptor 4 gene, FGFR4. Sequence variants in FGFR4 gene or haploinsufficiency has been suggested to associate with diverse phenotypes however not with CHI (12, 19).

A heterozygous mutation in the NSD1 gene (MIM 606680) identified in more than 75% of cases is a common genetic cause of Sotos syndrome (20). Previously, CHI was reported as an unusual presentation in Sotos patients (5, 21, 22), however a number of studies reporting CHI in this condition increased during last years (7, 8). Concurrent presence of NSD1 defects and CHI in Sotos syndrome has also been noticed. So, transient neonatal CHI was reported in Japanese patients with Sotos syndrome (7). Of 8 patients harboured a 5q35 microdeletion but only 3 of 8 required diazoxide treatment (7, 8). In national Japanese survey, CHI was present in about 10% children with Sotos syndrome, indicating strong association between these two features (23). Furthermore, CHI was reported in seven patients with Sotos syndrome caused by point mutations in NSD1 gene (24). In 3 of 7 patients CHI persisted for more than one year. These results challenge the previous hypothesis that CHI in Sotos syndrome is due to the deletion of additional genes in the 5q35 region. NSD1, itself is proposed to play a role in glucose homeostasis. NSD1 known as a histone methyltransferase is implicated in the regulation of chromatin and gene expression (6). Moreover, NSD1 is expressed in human pancreatic beta cells shown by bulk islet cell analyses and single-cell RNA-sequencing (19, 25, 26). Association between Sotos syndrome, response to diazoxide treatment and CHI disappearance over time was also described by Kapoor et al. though the exact mechanisms are still not completely understood (27).

Our case with resolved CHI that persisted for almost two years is in line with previous publications that reported a similar association between Sotos syndrome and CHI. The definition of transient hyperinsulinemic hypoglycaemia (HH) was poorly defined in earlier studies, and is characterised by spontaneously resolution within a few days to 6 months of life (27). According to the definition, the transient CHI is prolonged in our case. It is unclear if this can be due to a relatively large deletion. The patient required extra thorough feeding and for almost two years was on medication with diazoxide, a KATP channel opener, the first-line therapy for CHI (28). It is important to note that our patient responded severely to the diazoxide, which led to heart failure, therefore, diazoxide was reinitiated at a low dose, less than 5mg/kg/d because of risk for heart complications. Nevertheless, the doses were sufficient to avoid hyperinsulinemia and to ensure normoglycemia. Compare to our patient who required treatment with diazoxide for almost 2 years, diazoxide treatment for less time was previously reported. This period was up to 8 months of age (29) and three children with point mutations in NSD1 gene were treated over one year (6).

As practice shows, neonatal CHI needs the correct diagnosis and an adequate treatment in order to avoid neurological consequences. Our patient with Sotos syndrome presented a broad spectrum of clinical features, especially in the context of CHI. The identification of NSD1 abnormalities in most of Sotos patients makes a molecular diagnosis possible that confirms the clinical diagnosis of Sotos syndrome. Despite that hypoglycemia has been described as a minor feature in Sotos syndrome, several reports on a genotype-phenotype correlation were published that warrant further research in future. Our proposal is that, in neonatal diagnostics, the phenotypic spectrum of Sotos syndrome should include HI as a significant feature. Our case demonstrates that early clinical diagnosis of this rare condition is challenging and depends on the subjective experience and judgement. Experiences and lessons from our treatment procedure will merit inclusion within medical discourse, and this case report might serve as a reference for the diagnosis and treatment of similar patients in the future.

**Material 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 SD scores (SDS) were calculated using current National references (30, 31).
Molecular genetic analyses

Targeted next generation sequencing for with a congenital hyperinsulinism sequencing panel with copy number variation 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 99,5%. Following genes, ABCC8, GCK, GLUD1, HADH, HNF1A, HNF4A, SLC16A1, and UCP2 were analysed.

High resolution chromosomal microarray (CMA). Peripheral blood was collected in EDTA tubes using standard procedure, and DNA was isolated from 200 μL of whole blood using the QiaSymphony (Qiagen, Valencia, CA) according to the manufacturer's instructions. DNA was quantified using the NanoDrop 1000 Spectrophotometer (Thermo Scientific, Waltham, MA). CMA or genome-wide genotyping used for detection of copy number variations (CNVs) was performed with the Infinium CytoSNP-850K v1.2 Beadchip (Illumina, San Diego, California, USA) containing approximately 850,000 single nucleotide polymorphisms (SNPs) markers over the entire genome with an average probe spacing of 1.8kb. 200 ng DNA was hybridized on a beadchip after whole-genome amplification, followed by scanning on the HiScan (Illumina). Genotyping results were visualized, normalized and clustered using Genotyping module of the GenomeStudio software (Illumina) and by BlueFuse Multi software v.4.4. The cvnPartition 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 equal zero, and the BAF is 0.5. When a CNV is present, the LRR is non-zero, and the BAF is 0 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. Database of Genomic Variants (DGV), the Online Mendelian Inheritance in Man (OMIM), the dbVar Genome Browser and Database of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources (DECIPHER) were used to access known microdeletion and microduplication syndromes.

Fluorescence in situ Hybridization (FISH). 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 (CTNN2/RED in red) and 5p15.31 (UBE2QL1 in green) were used as control probes. The third probe in this mix was NSD1 specific probe on 5q35 labelled in green. The slides were dehydrated and 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 (DAPI) (Vysis). The images were captured by Leica Microscope and analyzed using Cytovision Image Analysis and Capture System (version 7.5) (Leica Biosystems, Mannheim, Germany).

Declarations

Ethics approval and approval for publication

Ethical approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent was obtained from the boy’s parents for the publication of any potentially identifiable images or data included in this article.

Data Availability Statement

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

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Author Contributions

EL and MB performed clinical examination. IG and MB analysed SNP-array data. EL, IG drafted the manuscript. IG prepared the figures. EL, EL and MB revised and edited the manuscript.

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List of abbreviations

GA - gestational age; NSD1 - Nuclear receptor-binding SET Domain containing protein; CPAP - continuous positive pressure therapy; NICU - neonatal intensive care units; EEG - electroencephalography; HH- hyperinsulinemic hypoglycaemia; CHI congenital hyperinsulinaemic hypoglycaemia

References


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)
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 Material 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.

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)
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| UNC5A    | unc-5 netrin receptor A              | 176810
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AR – autosomal recessive, AD-autosomal dominant. Genomic positions according GRCh38/hg38.