TITLE PAGE

Successful treatment of a cohort of infants with neonatal diabetes using insulin pumps including data on genetics and estimated incidence (20w)

Torun Torbjörnsdotter[1], Elisabeth Marosvari-Barna[1], Ewa Henckel[2,3], Martino Corrias[2], Svante Norgren[1,4], Annika Janson[1,4]

[1]Pediatric Diabetes Unit, Karolinska University Hospital, SE-141 86 Huddinge, Sweden

[2]Neonatal Intensive Care Unit, Karolinska University Hospital, SE-141 86 Huddinge, Sweden

[3]Division of Pediatrics, Department of Clinical Science, Intervention and Technology, Karolinska Institutet, SE-141 57 Huddinge, Sweden

[4]Division of Pediatric Endocrinology, Department of Women´s and Children´s Health Karolinska Institutet, SE-171 77 Stockholm, Sweden

Corresponding author:

Annika Janson, M.D., Ph.D.

ORCID 0000-0001-5106-5670

Pediatric Diabetes Unit, B 57 Albatross, Karolinska University Hospital,

SE-141 86 Huddinge, Sweden.

E-mail: annika.janson@sll.se, Phone: +46 727360455

Running head: Insulin pumps in neonatal diabetes

ABSTRACT (200w)

Aim: Neonatal diabetes is rare and treatment is challenging. We present aspects on treatment, genetics and incidence.

Method: This was a prospective cohort study including all cases in our study area in Sweden. We compared with data from the National Diabetes Registry, the Neonatal Quality Register and the National Patient Register.

Results: In the 19-year study period 1 January 1998 to 31 December 2016, we treated seven infants, five of them boys. Six patients used a subcutaneous insulin pump, and the smallest patient started at a weight of 938 grams. Most important was for the pump to deliver minute doses of insulin and the design of cannulas and tubing. All patients could stop insulin treatment at 17-145 days of age. One patient relapsed at age 4.5 years. Four patients used the insulin pump after discharge. A mutation was identified in five patients and this included all patients born after 30 weeks of gestation. The incidence of neonatal diabetes was 2/100000, higher than previously estimated for Europe. Similar but lower incidences were reported in the registries.

Conclusion: Insulin pumps were safe in neonatal diabetes. All seven cases were transient. Neonatal diabetes was more common in our area than reported from Europe.

Keywords: *ABCC8*; continuous glucose monitoring; insulin pump; neonatal diabetes mellitus; patient-centred care

Key notes (70w)

- Neonatal diabetes is rare but from this cohort of seven infants we suggest that the incidence is higher than previously described
- Insulin pumps were used from a patient weight of 1000 grams where the ability of the pump to deliver small doses of insulin and the size, length and insertion angle of tubing and cannula was important
- The technical devices enabled parents to continue treatment of their child at home

INTRODUCTION

Neonatal diabetes mellitus (NDM) is defined as diabetes with an onset before six months of age. NDM can either be transient (TNDM) or remain as permanent neonatal diabetes mellitus (PNDM). The prevalence of PNDM has been reported as one in 215000 children in Slovakia (1) and one in 260000 children in three other European countries; the UK, the Netherlands and Poland (2). Other authors have proposed that NDM is less rare, with the minimal incidence of NDM (PNDM and TNDM) in Italy estimated to one in 90000 (3). Also, a higher incidence of PNDM of one in 40000 has been reported from Oman where consanguineous marriages are more common (4, 5).

Among patients undergoing genetic testing, PNDM constitute 40-50% of cases of NDM (6). More than 30 different genetic causes have been described in any of the biological pathways that regulate glucose homeostasis by affecting mechanisms of insulin release or pancreatic development and sustainability. Some of the more common mutations can result in both TNDM and PNDM (6, 7). Children with TNDM can relapse and get diabetes again later in life (6, 8). In contrast to type 1 diabetes mellitus, autoantibodies are not identified in NDM except for in very rare syndromes affecting the immune system (9).

Hyperglycaemia in a preterm infant can be the result of immaturity, insulin resistance, infection or treatment, for example with intravenous glucose or steroids (10). Therefore, hyperglycaemia in a newborn infant that calls for treatment with insulin for at least 14 days is often used as a practical definition of NDM (11).

Children with NDM are often born small for gestational age. The likeliness of a mutation is reported to be high in preterm children, and even higher in full-term children with NDM. In a large study, mutations were found in 97/146 (66%) of preterm infants with NDM compared to 501/604 (83%) in children born ≥37 weeks (12). Although the genetic defect obviously was

present at birth, some children present at a few weeks or months of age with failure to thrive, dehydration or ketoacidosis (8).

Children with mutations in either of the genes, *ABCC8* or *KCNJ1,* encoding the potassium channel of the pancreatic beta-cell membrane, as well as children with NDM resulting from abnormalities in a region of chromosome six, 6q24, can be successfully treated with oral sulphonylurea or other oral anti-diabetic drugs (8, 13, 14). However, until results of genetic testing are available, insulin will be necessary to ensure growth and development in all infants with NDM.

Insulin pump treatment is in our Paediatric Diabetes Unit at Karolinska University Hospital, Sweden, standard care for type 1 diabetes mellitus with 65% of all patients aged 0-17 years in Sweden using an insulin pump (15). In our unit, insulin pumps are almost always used in onset of type 1 diabetes mellitus below two years of age. To our knowledge there are no controlled trials comparing different modes of delivering insulin to patients with NDM.

There are practical challenges when treating children with NDM with minute volumes of insulin to optimise metabolic control and yet avoid potentially dangerous hypoglycaemic events. Also, complications associated with the use of intravenous lines make the use of subcutaneous administration of insulin via an insulin pump an interesting alternative. In a review, Rabbone et al compiled information from 29 cases of NDM treated with insulin pumps, the smallest around 1200 grams body weight, and concluded that their review indicated that treatment with insulin pumps is safe and effective in NDM, and other studies have also contributed to this conclusion (16-18). Likewise, continuous glucose monitoring (CGM) using a subcutaneous sensor represents an attractive mode of glucose control in neonates where frequent blood sampling and matching with feeding patterns can be both difficult and disturbing for the child in the neonatal intensive care unit (NICU). We also

hypothesised that parents could be trained to handle the insulin pumps and CGM similar to standard practice for parents of children with type 1 diabetes mellitus. Parental involvement would shorten the period needed for hospitalisation and empower the parents in their care for their infant and encourage patient-centred care.

In this observational longitudinal prospective study, we have compiled information from seven newborn children with diabetes that we believe to constitute the total number of cases in our area for the 19-year study period. The aim of this study was to present practical aspects of treatment as well as results of genetic analyses for the patients. We also estimate the incidence on NDM in our setting and compare our data to the incidence of NDM reported in three Swedish quality registers: the Swedish National Diabetes Registry Swediabkids that includes almost 100% of children with all forms of diabetes in Sweden (15), the Swedish Neonatal Quality Register that collects information of all patients in neonatal care (19), and the National Patient Register by the National Board of Health and Welfare that collects data on inpatient diagnoses from all hospitals in Sweden.

PATIENTS AND METHODS

Study area

The health care of the capital city of Sweden, Stockholm, is administered by the Stockholm Region for an area with 2.3 million inhabitants (20). Deliveries almost exclusively take place at hospitals. The Karolinska University Hospital in three geographic locations, Danderyd, Huddinge and Solna, constitute three of the four paediatric university hospitals with neonatal intensive care in the region. All patients with NDM born at Karolinska University Hospital were treated at the hospital in Huddinge. Also, all patients that were born at Södertälje Hospital and in need of neonatal intensive care were referred to Karolinska University Hospital Huddinge.

Study population

Children with NDM that were treated from 1 January 1998 to 31 December 2016 at Karolinska University Hospital Huddinge were the study population.

Study cohort

This is an observational study of a clinical cohort. Seven children fulfilled the inclusion criteria: an onset of diabetes before six months of age and treatment with insulin for more than 14 days. We believe these patients constitute all cases in the hospitals that would have referred patients to us. A girl born in 1998 in gestational week 26 with a birth weight of 872 grams made us initiate this study. She was treated with intravenous insulin for 11 days. An insulin pump was not used and genetic analysis was not performed. As the patient did not fulfil inclusion criteria she was not included in this study, but the case prompted us to start collecting information on patients with NDM from 1998 onwards.

Insulin pumps and insulin

During the study period two different insulin pumps were used for NDM; MiniMed Paradigm Real-Time and Paradigm VEO (Medtronic, Kista, Sweden). Pumps were chosen for reliability and ability to deliver small volumes, 0 or 0.025 U of insulin per hour. We connected the pump to the patient with a MiniMed Silhouette infusion set (Medtronic, Kista, Sweden), using shortest available tubing length (45cm) and smallest available cannula (13mm) for all patients (Table 1). This infusion set was chosen as it allows a 30-45 degrees insertion angle, or less, aiming at placing the cannula in the thin layer of subcutaneous fat between the skin and the muscular fascia beneath.

In the study period three different brands of insulin were used in the pumps: short-acting Insulin Human, Humulin Regular 100 U/ml (Eli Lilly Sweden, Solna, Sweden), and rapid-acting insulins Insulin Lispro, Humalog 100 U/ml (Eli Lilly Sweden, Solna, Sweden) and Insulin Aspart, Novorapid 100 U/ml (Novo Nordisk Scandinavia AB, Malmö, Sweden). Initially we used a 2-step procedure to give 1 U/ml. For the later patients, Insulin Lispro was diluted with a diluent provided by the manufacturer in a one-step dilution 1:10 to give insulin 10 U/ml (Table 1).

Subcutaneous glucose monitoring

For the first patient included in the study in 2007 we used microdialysis to monitor subcutaneous glucose (CMA Microdialysis AB, Kista, Sweden). Ongoing development of devices made us use different systems for CGM in the study period: DexCom G4 and DexCom G5 (Nordicinfu Care AB, Nacka Strand, Sweden) and Guardian RealTime system with MiniMed Sof-Sensor or MiniLink Enlite sensor (Medtronic, Kista, Sweden). Plasma-glucose was analysed for calibration of CGM as per manufacturer's advice, usually twice a day. CGM devices were chosen due to availability and perceived reliability. For the later cases in the cohort we also analysed down-loaded comprehensive data of the CGM using a web-based interface (CareLink, Medtronic, Kista, Sweden).

Investigations

Data on birth weight, gestational age, sex, the parents' country of birth, treatment with insulin, use of insulin pumps and CGM was recorded. Analyses of plasma-glucose, serum-insulin, plasma-glucagon, faeces-elastase, serum-C-peptide and serum-autoantibodies were performed at the Karolinska University Hospital laboratory, Stockholm and Skånes Universitetssjukhus, Malmö, Sweden. Genetic analyses were performed at Molekylargenetisches Labor, Weisswasser, Germany, University of Southampton, Wessex, United Kingdom, and Skånes Universitetssjukhus, Malmö, Sweden and for the later cases at the University of Exeter, Exeter, United Kingdom using Sanger sequencing, 6q24 methylation analysis, and targeted next-generation sequencing of known neonatal diabetes genes.

All patients were followed at the Pediatric Diabetes Unit after discharge from the NICU. After terminating insulin treatment, parents were alerted to react to signs of diabetes and regular clinical evaluation with tests of glycosylated haemoglobin and plasma-glucose were performed to determine whether diabetes re-occurred in children with TNDM.

Incidence of neonatal diabetes mellitus

To estimate the incidence of NDM, we compared the number of cases with the total number of deliveries. We also compared our data with data from three national quality registers. Firstly, we analysed data from the Swedish National Diabetes Registry Swediabkids that registers almost 100% of all cases of diabetes in children 0-17 years old in Sweden and used onset before 6 months of age as a way of finding cases of NDM. Also, we analysed data from the Swedish Neonatal Quality Register that records neonatal outcome in Sweden. Finally, we retrieved data from the National Patient Register that collects all in-patient diagnoses in Sweden. Both the Swedish Neonatal Quality Register and the National Patient Register use

the Swedish version of the International Classification of Diseases (ICD-10-SE) and we searched for the ICD-10-SE code Neonatal Diabetes P70.2.

Ethics

This study was approved by the Regional Ethics Committee (2016/1:12). Permission to use photographs was granted by the parents.

RESULTS

Treatment with insulin, insulin pumps and CGM

Intravenous insulin was started within the first two weeks of life for six of the children. One patient was diagnosed later and started receiving insulin therapy at 41 days of age (Table 1). Following the initial intravenous treatment period, delivering insulin using an insulin pump and monitoring glucose values with CGM was used in six patients.

The insulin pump infusion set and the CGM sensor were placed on locations where subcutaneous fat was present, usually the thigh and the upper arm of the child. We did not put devices on the abdomen to avoid the risk of penetrating the peritoneal membrane. Preterm infants were kept on intravenous insulin until they reached a body weight of around 1000 grams to enable us to safely insert the infusion set in subcutaneous tissue. The smallest patient weighed 938 grams when starting treatment with an insulin pump at the age of 32 days (Figure 1).

For use in the pump, insulin was diluted as described by the manufacturer. A one-step dilution 1:10 to give a concentration of insulin 10 U/ml was used for the later patients in the cohort (Table 1). Settings of pumps do not allow for diluted insulin and pumps were marked to illustrate that the actual dose was 10% of displayed dose. Tubings were flushed with the pump disconnected from the patient twice a day to limit effects of degeneration of insulin in the tubes due to slow speed of infusion and the heat provided by incubators or warming mattresses. The insulin in the pump was changed every 24 hours and infusion sets were changed every third day.

Patients were treated with a basal rate of insulin in addition to bolus doses given at set glucose threshold values, for example 10 mmol/l, or at time of meal. Breastfed children were weighed before and after feeding to determine the bolus dose of insulin, using individual ratios for

need of insulin in relation to carbohydrate intake, estimating 7 g of carbohydrate per 100 g of breast milk (21).

Bolus doses were given after feeding or arbitrarily divided in two fractions, before and after feeding, that together made up the desired dose of insulin. A typical total daily dose of insulin was 0.3 U/kg body weight (range 0.2-1.4 (U/kg/day). Based on the CGM registrations, the meal boluses were adjusted and typically made up 70-80% of the total insulin. For a patient weighing one kilo, the basal dose could therefore be 0.0025 U/h which made the dilution of insulin described above necessary. When terminating treatment, the basal insulin administered by the pump was gradually lowered and stopped first, and the boluses kept until the child was not hyperglycaemic after meals.

The sensor for CGM was placed in subcutaneous tissue before or at the time of starting insulin pump treatment (Figure 2). The sensor was changed according to the manufacturer's recommendations after 5-7 days or earlier if the insertion place showed signs of skin irritation. Transparent self-adherent dressings were used to support the sensor and its cannula and yet allow inspection. The CGM readings were checked every hour until stabilised, and then before and two hours after every meal, if applicable. For patients on continuous feeding the sensor was checked every second hour. Goals for glucose control were set to 6-12 mmol/l at the start of treatment, regardless of whether the patient had meals or continuous feeding, and goals were narrowed to 4-8 mmol/l after a period individualised for each patient. We were unable to make comprehensive statistical analyses of glucose control, but an example of CGM registration and effect of insulin bolus doses is shown in Figure 3. The staff of the NICU staff was instructed to calibrate the CGM against plasma-glucose every eight hours, preferably when values were stable, and we expected a delay of 10 minutes for changes in plasma-glucose to be noticed by the sensor. Urine from each diaper was checked for ketones to determine the renal threshold for hyperglycaemia.

For safety, we developed routines and bed-side protocols for monitoring of pumps and CGM in collaboration between the NICU and the Pediatric Diabetes Unit.

No severe side-effects, such as severe hypoglycaemia or local infection was observed. Both parents and staff handled the technical devices well after initial training. No patient continued with subcutaneous injections or intravenous insulin after having used an insulin pump. Insulin pump treatment was terminated when insulin was no longer needed to maintain glucose within targets. Four patients left the NICU and continued treatment in their homes with insulin pumps with support from the hospital. The 24-hour technical support service by the manufacturers of pumps and CGM was useful. No patient was transferred to treatment with oral anti-diabetic drugs as results of genetic analyses were not available before the treatment with insulin was terminated.

Laboratory and genetic tests

Six investigated patients had none of the antibodies, Islet Antigen 2 or Glutamic acid decarboxylase commonly seen in type 1 diabetes mellitus, and one patient was not tested. Six patients had no blood-ketones at diagnosis and patient one was not tested for ketones. Results on serum-insulin, plasma-glucagon and faeces-elastase were not complete or difficult to interpret due to unclear relation to plasma-glucose and nutrition (data not shown).

A mutation was identified in five patients (Table 1) and this included all patients born after 30 weeks of gestation. No mutations were identified in the two most preterm patients; analyses for mutations in *KCNJ11*, *ABCC8* and *INS* were negative in patient one and mutations in *KCNJ11*, *ABCC8, GK, HNF1 alfa* and *HNF4 alfa* or alterations in 6q24 were not identified in patient two. Patients five and six were siblings with an identical 6q24 paternal duplication and

the same mutation could be identified in the father and paternal grandfather. The remaining three children had an *ABCC8* mutation (Table 1). The mutation in patient three was previously known and was identified also in the patient´s father, whereas the mutation found in patient four was novel and identified also in the patient´s father with diabetes and therefore likely associated with NDM. The mutation in patient seven was a novel missense mutation where other genetic abnormalities were not identified.

Two children had one or both parents born outside a Nordic (Denmark, Finland, Iceland, Norway, Sweden) country: the parents of patient one were born in Iraq and related, and patient four, with likely paternal inheritance of NDM, had a mother from Colombia.

All patients could be taken off insulin and were diagnosed as TNDM. To date, patient five was diagnosed with diabetes again at 4.5 years of age. A developmental delay was suspected in patient seven, but the patient moved from the area and was not available for investigation or follow up. No patient was diagnosed with a syndrome associated with NDM.

Incidence of Neonatal Diabetes

In the 19-year study period 1 January 1998 to 31 December 2016 seven cases of neonatal diabetes were treated at our clinic (Table 1). The number of deliveries in the four obstetric clinics that would refer patients to us in the 19 years of the study were 306637 (20). We were unable to take into consideration if children were twins, early deaths or stillbirths. Around 1% of deliveries are multiple births which would add 3000 children to the figure and we used an estimated total number of births 310000 for our calculations. This corresponds to an estimated incidence of NDM of one in 45000 children. In the Swedish National Diabetes Registry Swediabkids a total number of 17 children with an onset of diabetes before six months of age were registered in Sweden in the available period 1 May 2005 to 31 December

2016 (11.5 years). All patients in this study were included. In Sweden, a total number of 1337165 children were born from 1 January 2005 to 31 December 2016 (22) and this corresponds to an incidence of neonatal diabetes of one in 80000 children. In the Swedish Neonatal Quality Register and the National Patient Register, analyses could be made for the respective hospitals. The Swedish Neonatal Quality Register identified six cases and the National Patient Register identified five cases of NDM from the hospitals in the study area. No patient that was not included in our study was identified, hence supporting that our study recorded all cases in the study area.

DISCUSSION

NDM is a heterogenous disease where a genetic mutation can be identified in more than 80% of cases. Looking at large series of children with NDM undergoing comprehensive genetic testing, about 50% are TNDM, 40% PNDM and 10% syndromic (6,23). The incidence of NDM in our study was one in 60000 if we only considered the five cases where a mutation was identified, or one in 45000 if we also include cases where a mutation was not identified, and relate this to all births in the study area during the 19 years of study. In our study, the incidence of NDM was therefore higher than the minimal incidence of one in 90000 reported from Italy (3) and much higher than previously reported from Europe (1-2). In the comparison we made in Swedish quality registers, the reported incidence of children with diabetes with an onset before six months of age from the Swedish National Diabetes Registry Swediabkids was one in 80000. The hospital-based quality registries, the Swedish Neonatal Quality Register and the National Patient Register had a slight under-reporting as one and two of the cases in this study were missing in each register, respectively. We therefore conclude that the incidence of one in 45000 that we report in this study represent a minimal incidence that could be slightly higher if cases were missed by the study and the three quality registries. On the other hand, all cases in our study were TNDM. The variation in incidence and proportion of TNDM to PNDM may reflect referral biases such as patients with TNDM to a lesser extent being identified and referred for testing, as well as true variations in these hereditary conditions.

Clinicians should be aware of NDM. In our study mutations were identified in all cases born from gestational age 30 weeks. In the literature, it is pointed out that also among the most premature children with NDM, about one in three has a mutation (12) and hence genetic analysis should be performed for all cases. Genetic diagnosis is helpful for the family to evaluate the situation and prognosis, including the risk for later diabetes in cases that turn out

to be TNDM. Most importantly, a genetic analysis also identifies the children where insulin can be replaced by superior treatment with sulphonylurea in oral preparations (8).

In modern neonatal care, parents are much involved in the care of their infant, also in the high technology setting of the NICU and this is regarded beneficial to the family and their child (24). This patient-centred care is also a part of modern paediatric diabetes care and parents of the children with NDM were gradually taught to use the insulin pump and CGM. Four patients were able to go home while still using these technical devices. We developed structures for safe care and handling of insulin pumps in the NICU (guidelines and bed-side reports) and efforts were made to collaborate with the high number of staff that is involved in the care of an infant in the NICU. In Sweden, the cost of these devices is covered by the public health care and costs were therefore no issue for the individual families.

In conclusion, we argue that using the technical devices, that are part of standard care for patients with type 1 diabetes mellitus, is safe in children with NDM and promotes improved glucose control. It also reduces the problems of intravenous access and frequent blood sampling. Some of the staff, but not all, need to have high technical skills, experience and familiarity with the technology used. The most important practical features were ability of the pump to deliver small doses of insulin and the size, length and insertion angle of cannulas and tubing. Also, NDM was more common than previously reported. Further studies providing detailed data on metabolic control, growth and comparisons between different treatments modules would be very beneficial to aid clinicians treating these rare cases.

Strengths and limitations

The strength of this study was that we described incidence and a technical development over almost two decades. We used a known number of deliveries as our denominator. A limitation was that although we claimed to have identified all cases from 1998 when we started collecting the information, cases may have been missed which would make the incidence higher. Also, in the Swedish National Diabetes Registry Swediabkids cases of PNDM may have been more likely to be included than TNDM, but this also would have resulted in a higher incidence. The three quality registries have all become more accurate with time but there may have been under-reporting, at least in the earlier years which also would have increased incidence. Two patients in our study were siblings which may have inflated our figures by one case and compensating for this would result in a minimal incidence of four cases with mutations in 310000 births, which resembles the Italian data (3). During the study period, there was a technical development that led us to use various technical devices and for each patient we chose what seemed most convenient and appropriate among available devices at the time.

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CONFLICTS OF INTEREST

None of the authors have conflicts of interest to declare.

ABBREVIATIONS

CGM	Continuous glucose monitoring
ICD-10-SE	International Classification of Diseases, version Sweden 10
NDM	Neonatal diabetes mellitus
NICU	Neonatal intensive care unit
PNMD	Permanent neonatal diabetes mellitus
TNDM	Transient neonatal diabetes mellitus

REFERENCES

1. Stanik J, Gasperikova D, Paskova M, Barak L, Javorkova J, Jancova E, et al. Prevalence of permanent neonatal diabetes in Slovakia and successful replacement of insulin with sulfonylurea therapy in KCNJ11 and ABCC8 mutation carriers. *J Clin Endocrinol Metab.* 2007 Apr;92(4):1276–82.

2. Slingerland AS, Shields BM, Flanagan SE, Bruining GJ, Noordam K, Gach A, et al. Referral rates for diagnostic testing support an incidence of permanent neonatal diabetes in three European countries of at least 1 in 260,000 live births. *Diabetologia* 2009 Aug;52(8):1683–5.

3. Iafusco D, Massa O, Pasquino B, Colombo C, Iughetti L, Bizzarri C, et al. Minimal incidence of neonatal/infancy onset diabetes in Italy is 1:90,000 live births. *Acta Diabetol*. 2012 Oct;49(5):405–8.

4. Bappal B, Raghupathy P, de Silva V, Khusaiby SM. Permanent neonatal diabetes mellitus: clinical presentation and epidemiology in Oman. *Arch Dis Child Fetal Neonatal Ed.* 1999 May;80(3):F209-212.

5. Al Senani A, Hamza N, Al Azkawi H, Al Kharusi M, Al Sukaiti N, Al Badi M, et al. Genetic mutations associated with neonatal diabetes mellitus in Omani patients. *J Pediatr Endocrinol Metab*. 2018 Jan 26;31(2):195–204.

6. De Franco E, Flanagan SE, Houghton JAL, Lango Allen H, Mackay DJG, Temple IK, et al. The effect of early, comprehensive genomic testing on clinical care in neonatal diabetes: an international cohort study. *Lancet* 2015 Sep 5;386(9997):957–63.

7. Touati A, Errea-Dorronsoro J, Nouri S, Halleb Y, Pereda A, Mahdhaoui N, et al. Transient neonatal diabetes mellitus and hypomethylation at additional imprinted loci: novel ZFP57 mutation and review on the literature. *Acta Diabetol.* 2019 Mar;56(3):301–7.

8. Hattersley AT, Greeley SAW, Polak M, Rubio-Cabezas O, Njølstad PR, Mlynarski W, et al. ISPAD Clinical Practice Consensus Guidelines 2018: The diagnosis and management of monogenic diabetes in children and adolescents. *Pediatr Diabetes* 2018;19 Suppl 27:47–63.

9. Chatila TA, Blaeser F, Ho N, Lederman HM, Voulgaropoulos C, Helms C, et al. JM2, encoding a fork head-related protein, is mutated in X-linked autoimmunity-allergic disregulation syndrome. *J Clin Invest.* 2000 Dec;106(12):R75-81.

10. Sinclair JC, Bottino M, Cowett RM. Interventions for prevention of neonatal hyperglycemia in very low birth weight infants. *Cochrane Database Syst Rev.* 2009 Jul 8;(3):CD007615.

11. Ogilvy-Stuart AL, Beardsall K. Management of hyperglycaemia in the preterm infant. *Arch Dis Child Fetal Neonatal Ed*. 2010 Mar;95(2):F126-131.

12. Besser REJ, Flanagan SE, Mackay DGJ, Temple IK, Shepherd MH, Shields BM, et al. Prematurity and Genetic Testing for Neonatal Diabetes. *Pediatrics* 2016;138(3).

13. Babiker T, Vedovato N, Patel K, Thomas N, Finn R, Mannikko R, et al. Successful transfer to sulfonylureas in KCNJ11 neonatal diabetes is determined by the mutation and duration of diabetes. *Diabetologia* 2016 Jun;59(6):1162–6.

14. Bowman P, Sulen Å, Barbetti F, Beltrand J, Svalastoga P, Codner E, et al. Effectiveness and safety of long-term treatment with sulfonylureas in patients with neonatal diabetes due to KCNJ11 mutations: an international cohort study. *Lancet Diabetes Endocrinol.* 2018;6(8):637–46.

15. Åkesson K, Eriksson E, Fureman A-L, Gudbjörnsdottir S, Hanberger L, Pundziute-Lyckå A, et al. Swediabkids, årsrapport 2018 (Swediabkids, annual report 2018); Accessed July 12th, 2019. Available from: www.ndr.nu/pdfs/Arsrapport_Swediabkids_2018.pdf

16. Rabbone I, Barbetti F, Gentilella R, Mossetto G, Bonfanti R, Maffeis C, et al. Insulin therapy in neonatal diabetes mellitus: a review of the literature. *Diabetes Res Clin Pract*. 2017 Jul;129:126–35.

17. Bharucha T, Brown J, McDonnell C, Gebert R, McDougall P, Cameron F, et al. Neonatal diabetes mellitus: Insulin pump as an alternative management strategy. J *Paediatr Child Health* 2005 Oct;41(9–10):522–6.

18. Olinder AL, Kernell A, Smide B. Treatment with CSII in two infants with neonatal diabetes mellitus. *Pediatr Diabetes* 2006 Oct;7(5):284–8.

19. Norman M, Källén K, Wahlström E, Håkansson S, SNQ Collaboration. The Swedish Neonatal Quality Register - contents, completeness and validity. *Acta Paediatr.* 2019 Aug;108(8):1411–8.

20. Stockholm Region website and personal communication Gunilla Berg, Stockholm Regional administration; Accessed July 5th, 2019. Available from: www.sll.se

21. Stoltz Sjöström E, Ohlund I, Tornevi A, Domellöf M. Intake and macronutrient content of human milk given to extremely preterm infants. *J Hum Lact.* 2014 Nov;30(4):442–9.

22. Födda i Sverige (Born in Sweden). Statistics Sweden; Accessed June 29th,2019. Available from: www.scb.se

23. De Franco E. Personalised medicine in neonatal diabetes. Presentation at the "Hot Topics in Endocrinology": May 3, 2018; Stockholm, Sweden.

24. Flacking R, Breili C, Eriksson M. Facilities for presence and provision of support to parents and significant others in neonatal units. *Acta Paediatr.* 2019 Jul 26;

TABLE 1. Characteristics of patients in order of increasing birth weight

Patient	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Gestational age	24+2	26+1	30+0	34+4	38+3	39+3	42+0
Birth year	2016	2010	2007	2014	2007	2011	2012
Sex	Male	Male	Male	Female	Female	Male	Male
Birth weight (grams)	642	777	1455	1881	2200	2355	3500
Small for gestational age	No	Yes	No	Borderline	Yes	Borderline	No
pH at diagnosis	7.08	Normal	Normal	Normal	Normal	Normal	Normal
C-peptide at diagnosis (reference 0.25-1 nmol/l)	0.43	0.35	0.06	0.72	0.21	0.28	Missing value
Plasma-glucose at diagnosis (reference <11 mmol/l) [reference <200 g/dl)	31 [558]	19 [342]	19 [342]	28 [504]	11 [200]	14 [252]	28 [504]
Age at start of insulin (days)	1	12	4	2	4	5	41
Age at start of insulin pump (days)	45	54	7	13	9	5	43
Age at stopping insulin (days)	59	57	145	17	50	22	116
Insulin and concentration in pump (U/ml)	Aspart 10	No pump	Human Regular 1	Lispro 100	Lispro 10	Aspart 10	Aspart 100
Insulin pump	Paradigm Veo	No pump	MiniMed 515	Paradigm Veo	Paradigm RT	Paradigm Veo	Paradigm Veo
Pump infusion set	Silhouette	No pump	Silhouette	Silhouette	Silhouette	Silhouette	Silhouette
Continuous glucose monitoring system	DexComG5	MiniLink	Microdialysis	MiniLink	MiniLink	MiniLink	MiniLink
Glucose sensor	DexComG4	Sof	Microdialysis	Enlite	Sof	Enlite	Sof
Genetic mutation	Not identified	Not identified	*ABCC8* R1380C	*ABCC8* c.4503C>A	6q24 paternal duplication	6q24 paternal duplication	*ABCC8* c.3916G>A

FIGURE LEGENDS

Figure 1. Patient 1 at 938 g at onset of treatment with insulin pump (Medtronic Veo) on upper arm and Continuous Glucose Monitoring (DexCom5) on leg. Shown with permission from parent.

Figure 2: MiniLink in right thigh of patient number 4. The diaper of the child is to the right and the examiner holds the knee. Shown with permission from parent.

Figure 3: Computer download for patient six showing effect of bolus doses given with insulin pump at meals and resulting effect on glucose measured with continuous glucose monitoring. The patient no longer has a basal insulin dose. Note that insulin was diluted 1:10 and actual daily dose was 0.17 U.

AUTHORS´ CONTRIBUTIONS

All authors were involved in the clinical care of the patients at different points in time. TT collected longitudinal data from patients. AJ drafted and wrote the manuscript in collaboration with TT and EH. All authors contributed and accepted the final version of the manuscript.