Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

Diagnosis and management of neonatal diabetes mellitus: A survey of physicians' perceptions and practices in ASPED countries

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ARTICLE INFO

Article history:
Received 13 October 2019
Accepted 3 December 2019
Available online 10 December 2019

Keywords:
Neonatal diabetes
Children
Neonates
Genetic testing
Survey
Practices
Knowledge
Attitudes
Monogenic diabetes

ABSTRACT

Aim: To ascertain the awareness and practice of neonatal diabetes mellitus (NDM) among paediatricians in Arab countries.
Methods: An online questionnaire was distributed to physicians associated with the Arab Society for Paediatric Endocrinology and Diabetes (ASPED).
Results: We received 126 replies, from 16 countries. All except one classified the survey's case scenario as NDM and 94% agreed that NDM patients should have detailed assessment to identify extra-pancreatic features. Although 92% felt that genetic testing is necessary, only 72% requesting them routinely and 32% unaware of the availability of free genetic testing. Insulin is considered the initial therapy for 93% and 80% diluted insulin to deliver accurate doses. Basal-bolus regimen was preferred by 36% and similar percentage used insulin pump. The remaining 28% favour long acting insulin alone. Oral sulfonylureas would be tried empirically by 34% and 69% would do so if genetic testing is unavailable. Whilst 70% have no local NDM management guidelines, 41% are unaware of any international guidelines.
Conclusions: The ASPED surveyed clinicians have good awareness of NDM diagnosis with marked variation in their practice raising the need to establish management guideline for the condition. The survey highlights areas to focus on in developing consensus and educational activities.

1. Introduction

Neonatal Diabetes Mellitus (NDM) refers to diabetes diagnosed within the first 6 months of life. It can be permanent (PNDM) or transient (TNDM) and both forms can be an isolated finding or in association with other features [1]. Some patients with TNDM can go into remission and relapse few years later [2]. Mutations in more than 20 genes, that control the pancreatic beta cell function or development, have been identified in over 80% of affected individuals [3,4]. Most TNDM

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https://doi.org/10.1016/j.diabres.2019.107975
0168-8227/

patients have imprinting defects of chromosome 6q24 [2,5] while the genotype of PNDM is largely influenced by paternal consanguinity [1,4]. Heterozygous mutations in the KATP channel genes (*KCNJ11* and *ABCC8*), are the commonest cause of PNDM in outbred populations [3,6], whereas, in high consanguineous populations, like Arabs, PNDM is more likely due to recessive EIF2AK3 mutations [7,8]. The majority of patients with KATP channel mutations and a few with chromosome 6 - related TNDM achieve better glycaemic control by oral sulfonylurias (SU) than insulin [9–11] while some subjects with biallelic *SLC19A2* mutations can be off insulin following thiamine therapy [12]. Knowledge of the genetic aetiology can also help predicting the course of NDM and guide early detection of other features.

NDM is rare but its highest incidence was reported from the Arab populations of northwest Saudi Arabia (1:21,000) [7] and UAE (1:31,000) [13], compared to the highest rate of 1: 90,000 reported from Europe [14]. Given the rarity of NDM, some clinicians may have limited awareness of the condition or the importance of genetic testing in its management. Consequently, patients may have delayed diagnosis or being mismanaged as type 1 diabetes. Furthermore, knowledge of the physicians' awareness and practice of rare conditions can help in identifying areas to focus on when setting curriculum for educational activities or developing consensuses or clinical practice guidelines. To the best of our knowledge, there is no study assessing the clinicians' practice and awareness of NDM.

The aim of this survey is to ascertain the knowledge, attitudes and practices of paediatricians looking after children with diabetes and practicing in Arab Society for Paediatric Endocrinology and Diabetes (ASPED) countries regarding the diagnosis, and management of NDM

2. Subjects, materials and methods

2.1. Study design

This cross-sectional electronic survey was conducted between 14th November 2018 and 14th February 2019 under the ASPED auspices and approved by its research committee. A web-based commercial software (Survey Monkey, Palo Alto, CA, USA) was used. The target population was identified from the ASPED physicians' database. Respondents were asked to describe themselves in terms of specialties, age group, duration and volume of practice. They all received an initial invitation e-mail that explained the rationale and what was required from the respondents, followed by 4 reminder e-mails over the study period including unique e-mail-specific electronic links to the questionnaire. The voluntary nature of the exercise and the strict confidentiality in which data will be analysed were reiterated. At the end of the study, survey responses were collected anonymously, stored electronically, and analysed. Summary statistics were prepared for responses to each question with percentage adjustment to account for missing responses. The survey was provided in both English and French. A formal approval for survey was granted by the IRB of Sheikh Khalifa Medical City (being the institution from which the surveys were dispatched). All subjects provided an explicit informed consent electronically to voluntary participate before they could proceed to the actual survey questions.

2.2. The survey questionnaire

The survey questions were developed de novo to address the objectives of the study. The instrument reiterates the full information provided in the invitation email described above. The respondents were then asked to confirm consent to participate. Only those who confirm consent are allowed to proceed to the rest of the questions. The respondents' demographic and professional profiles are captured by three questions: How do you best describe yourself? What professional grade are you? and in which country do you currently practice? Following this, consenting respondents could proceed to the "The Neonatal Diabetes Mellitus (NMD) Questionnaire" (Table 1). The questionnaire had 30 multiple choice questions based on a typical case scenario (Box 1).

2.3. Statistical analysis

Results are adjusted as percentages to take account of the missing responses. Comparisons were tested using t-tailed Fisher's exact test when appropriate. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Response rate and respondents' characteristics

A total of 516 invitations were sent out; 11 emails were not delivered. 306 opened the invitation and 151 responded, of which 126 (24.4%) respondents agreed to take part in the survey. Eighty-nine (71%) were paediatric endocrinologist, 24 (19%) were paediatricians with interest in diabetes and 13 (10%) were trainees in paediatric endocrinology and diabetes. The largest number of respondents were from Saudi Arabia [25] followed by Egypt [20] Iraq [16], UAE [15], Algeria [11], Palestine and Oman (6 each), Jordan and Libya (5 each), Lebanon [4], Bahrain and Kuwait (3 each), Morocco, Tunisia, and Sudan (2 each) and Qatar [1].

3.2. Diagnosis and evaluation (SuppInfo Table 1)

All 126 participants except one agreed that the described scenario is enough for making the diagnosis of NDM with 75% of them were unable to predict whether the patient will have TNDM or PNDM. Most (94%) agreed that patients with NDM should have detailed phenotypic, radiological and laboratory assessment to identify extra-pancreatic features. 92% felt that genetic testing is indicated for infants with diabetes with discrepancy in the cut off age of the presentation at which genetic testing should be conducted. 53% of responders agreed with 6 months while 29% felt that the cut off age should be extended to 12 months. Only 72% request genetic testing. Barriers for genetic testing included 96% cost and logistic such as transportations, long time to get results 13%, 7% felt it is not clinically relevant. 68% are aware of

Table 1 – The Neonatal Diabetes Mellitus (NMD) Questionnaire with the response options in square brackets [].

Please read the case scenario (Box 1) and then give your answer based on what would you do rather what should be done:

Q1. Do you agree that this child's diabetes is neonatal diabetes mellitus? [Yes; No].
Q2 Can you predict whether his NDM will be permanent or transient? [Yes, No].
Q3 What would be your next treatment step for this child? [start insulin, start diet and calories restriction only, try a sulfonylurea (SU)].
Q4 If insulin was chosen; how much would you give (IU/kg/day)? [0.2–0.3, 0.4–0.5, 0.6–0.7, 0.8–1.0, greater than 1.0].
Q5 Would you dilute insulin? [Yes, No].
Q6 What would you use to dilute the insulin? [Distilled water, normal saline, 5% dextrose, any of the above].
Q7 Which insulin regimen would you use? [Multiple daily injection as a basal/bolus regimen, continuous subcutaneous insulin infusion (insulin pump), Intermittent Short acting insulin, long acting insulin only].
Q8 Which short acting insulin would you use? [Analogue, regular, no preference].
Q9 Which basal insulin would you use? [Glargine, Detemir, NPH, Degludec].
Q10 What percentage of the total insulin requirements would you give as basal insulin? [20–30%, 30–40%, 40–50%, 50–60%, 60–70%].
Q11 While taking history, do you check if parents are consanguineous, any sibling death or a child with a similar condition in the family? [Yes, No, I do not think it is relevant, but just routine questions].
Q12 In clinical assessment, what features would you look for? (you can tick more than one) [Developmental delay/neurological deficit as seizures, hepatosplenomegaly, dysmorphism, skeletal deformities, cardiac malformation, glaucoma, nothing specific].
Q13 What further test(s) would you request for this child? (you can tick more than one) [Nothing specific, Skeletal survey, thyroid function test, liver and kidney functions, full blood counts, echocardiography, hearing assessment, abdominal imaging (US, CT or MRI)].
Q14 Do you think all infants with diabetes require genetic testing? [Yes, No].
Q15 If you answered Yes in the previous question, what is your cut-off age at diagnosis to request genetic testing (in months)? [6,9,12]
Q16 Do you request genetic tests for all your infants with neonatal diabetes? [Yes, No]
Q17 If you do not request genetic tests for all your infants with neonatal diabetes; Why not? (you may tick more than one) [cost/logistic difficulties, clinically not, takes long time to receive the results]
Q18 Are you aware of the availability of free genetic testing under research funding arrangements? [Yes, No].
Q19 To what extent do you agree with this statement? "*Genetic testing for NDM is important because it identifies patients who can be treated with Sulfonylureas instead of insulin*" [strongly agree, agree, neutral, disagree, strongly disagree]
Q20 Would you try a Sulfonylureas while waiting for the results of genetic testing? [Yes, No].
Q21 Would you try Sulfonylureas if you have no facilities for genetic testing? [Yes, No].
Q22 Would you try Sulfonylureas before sending for genetic testing? [Yes, No].
Q23 A successful Sulfonylureas dose is likely to range from: [0.01–0.1 mg/kg, 0.1–1.0 mg/kg, I can't remember but will check the dose before use. no specific dose, just a trial and error].
Q24 How many patients with NDM diagnosed less 6 months old did you see/do you have in your clinic? [Less than 5, 5–10, 10–15, greater than15].
Q25 What is the commonest causes of NDM in your clinic? [KATP channel mutations (KCNJ11 & ABCC8), EIF2AK3 mutations (Wolcot Rallison syndrome), Insulin gene (INS) mutations, I don't know].
Q26 Do you think it is important to develop regional/international guideline for the management of NDM? [Yes, No].
Q27 Do you have a guideline for the management of NDM in your unit? [Yes, No].
Q28 Are you aware of any international guidelines for the management of NDM? [Yes, No].
Q29 Do you see more hypoglycaemia in infants with NDM compared to older children? [Yes, No].
Q30 If you do see more hypoglycaemia in infants with NDM compared to older children; what do you advise families to decrease the risk of hypoglycaemia in those infants? [Routinely give corn starch or similar at bedtime, give extra milk bottle at bedtime, nothing special apart from the general advice].

The order of the questions is as presented in the questionnaire. The responses results are presented in a thematic structure to serve the discussion.

Please read the following case scenario and then give your answer based on what would you do rather what should be done:
"A two months old boy presented with vomiting and poor feeding. His blood pH was 7.21, random blood glucose 260 mg/dl (14.4 mmol/L) and urine was 3 + for glucose and ketone. He was started on iv fluid and insulin infusion. 24 hrs later his symptoms improved and pH normalized; but he still has hyperglycaemia and glycosuria."

availability of free genetic testing. Pediatric endocrinologist were more aware of availability of free genetic testing on research funding compared to general paediatricians with interest (76% vs 53%, p = 0.012).

3.3. *Insulin therapy (SuppInfo table 2)*

In total, 93% of responders used insulin as initial therapy. A starting dose of 0.5 iu/kg or less was recommended by 85%, while 6% would try SU and one responder would use diet alone. Of the responders 80% diluted insulin and 84% would use normal saline. Multiple daily injection as a basal/bolus regimen was used by 36% and similar percentage used pump while the remaining 28% preferred long acting insulin alone. Over all 72% used insulin analogue than regular with 44% still using NPH as basal insulin. There was a variation on the percentage of basal insulin with more than 50 percent of the total daily insulin dose is given as basal insulin in 27% of respondents.

3.4. *Role of sulfonylurea treatment (SuppInfo table 3)*

The majority of the participants (94%) agreed that genetic testing is important to identify patients who can benefit from SU therapy. Pediatric endocrinologist were more aware of this fact than pediatricians with interest in diabetes. (96 vs 89%). 34% would try SU before genetic testing while 69% will do so if there no facilities for genetic testing. 42% will try it while waiting for the results of genetic testing.

3.5. *NMD in practice (SuppInfo table 4)*

Of the 123 respondents, 46% have more than 5 patients in their clinics and 58% don't know the genetic cause of their NDM patients. 70% have no guidelines to manage NDM and 41% are not aware of any guidelines. However, 99% felt the need to develop regional/international guideline for the management of NDM

3.6. *Hypoglycaemia (SuppInfo table 5)*

67% reported higher rate of hypoglycaemic events in NDM compared to older infants and their advice on its prevention varied with 48% recommended families to give infants extra milk bottle at bedtime.

4. Discussion

We report the first survey of the knowledge and practice of physicians looking after children with NDM. The study reflects the opinion of more than 120 pediatricians practicing in 16 countries where this form of diabetes is more frequent than other parts of the world. The majority of the responders were experienced physicians and around half of them have more than 5 children with this rare condition in their clinics. The bilingual nature of the questionnaire allowed clinicians from all ASPED countries to participate including 3 North African countries, where French is the language used for professional communication.

It is reassuring that almost all responders classified the described case as NDM and indicated that infants with NDM should have detailed assessment to identify extra-pancreatic features. Their high awareness of the condition was also illustrated by the fact that most of them were familiar with the clinical utility of genetic testing in NDM. However, there was a variation in the management between clinicians. This could reflect difference in training and level of experience among physicians or local resources and set ups.

Surprisingly, 70% of responders have no local guidelines for the management of NDM and 41% are not aware of any international guidelines. Although a number of consensus and clinical management guidelines are available for the practical management of common forms of childhood diabetes, the only published document on NDM was within the ISPAD guidelines for monogenic diabetes [4]. However, that guideline didn't focus on the challenge of insulin treatment in NDM. Almost all our responders highlighted the need to develop a regional/international guideline for the practical management of NDM and a recent review indicated that data on the insulin therapy in NDM is limited [15]. Most clinicians in this survey indicated that insulin is their first line of therapy and more than 80% of them diluted insulin, using normal saline, to deliver small doses. However, there was no consensus on the insulin type, regimen and mode of delivery. Insulin delivery in small infants is a challenge as the requirement is small, absorption is variable, the risk of dose error due to unavailability of ready-made diluted insulin is high and there are limited data for dilution of commercially available insulin preparations [15,16]. Although insulin pump therapy appears to be effective at this age group [16–18] only 36% of participants used pump for NDM, possibly due to limited resources in some countries. Interestingly, only 58% of surveyed physicians used insulin analogues, with more pediatric endocrinologists in favour of its use than pediatricians with interest in diabetes (67% vs 37%; p = 0.011). This could reflect local availabilities or concern of the risk of hypoglycaemia due to the rapid absorption of analogues coupled with the unpredictable feeding pattern at this age group. [19]

More than 90% of the responders agreed that the identifying the genetic cause of NDM can guide the most appropriate management for patients; however, only 72% of them routinely request genetic testing for their patients. Although a number of international laboratories offer free genetic testing for NDM on a research bases [4], around one third of the responders are not aware of this and they considered the cost of testing as the main barrier for not offering this service for their patients. More awareness about the availability of free genetic testing and/or providing facilities for conducting these tests locally are needed to improve the care of these children. It is recommended that patients diagnosed with diabetes within the first 6 months of life should have genetic testing [4]; however, some data indicated that extending the cut off age to 12 months may detect more children with identifiable genetic causes in those with negative autoantibodies [20,21]. Whilst 56% of responders agreed that the 6 months is a reasonable cut off point, around one third felt that the cut off should be extended to 12 months.

Previous report indicated that *EIF2AK3* mutation that cause WRS are the main cause of PNDM in Arab populations compared to other populations where KATP mutations are the commonest cause [8]. However, 28% reported KATP channels as a cause of NDM in their cohort. Because the majority of patients with these mutations are better managed with SU than insulin, it has been suggested that empirical inpatient trial of SU before genetic testing results are available is safe option in these patients [22]. In this survey, 42% of physicians agreed with this opinion while 69% will do so if there is no facilities for genetic testing and 34% would try it even before sending samples for genetic testing. As facilities for free genetic testing are now more accessible, we feel that the empirical trial of SU in all patients with NDM is not justified, particularly in areas with high consanguinity, such as Arab countries, where the KATP channel mutations are not a common cause of NDM.

Our study has some limitations. first it is a survey-based study rather than an accurate assessment of the real practices and outcome. Second, the response rate was not huge. This may reflect a variation in the research interest, and confidence in the conclusions of survey-based studies. It is also possible that given the rarity of the condition some of the non-responders have no NDM patients in their clinics and thus opted out of the survey. However, the responders were from the 16 ASPED countries reflecting wider opinions from the Middle East and North African.

In summary, this survey showed that pediatricians caring for children with diabetes in ASPED countries have good awareness on the diagnosis of NDM and the clinical utility of genetic testing in its management. However, there was a wide variation in their clinical practice. The findings of this survey provide a baseline overview of the current clinical practice in the area which would be useful in informing regional interdisciplinary discussions to develop regional guidelines in collaboration with international organizations and direct continuous professional developments activities.

Acknowledgment

The authors would like to express their gratitude to all respondents who shared their expertise and opinions by participating in the survey.

Authors' contribution

AMH, NA, AD conceived the research idea and developed the questionnaire. SAB revised the questionnaire and managed the online survey and data extraction. All authors had access to all the raw data. AMH drafted the manuscript, and all authors revised it and approved its final version.

Funding

This study received no specific funding.

Declaration of Competing Interest

None of the authors has any conflict of interest.

Compliance with ethical principles

This article does not contain any studies with human or animal experiments performed by any of the authors. However, the study was approved by The Institutional Review Board of Sheikh Khalifa Medical City, Abu Dhabi following its local, regulations. All participants provided electronic informed consent before they could proceed to the survey.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.107975.

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