Newborn Screening for Diabetes Research

Subjects: Others
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This study explores the use of newborn screening in diabetes research, considering the overlap between metabolic networks in diabetes and inborn errors of metabolism. It compares dried blood spots collected between 24-72 hours at birth (up to 5 days) and cord blood, collected at birth. Both samples yield and complement different kinds of information. Cord blood may reflect maternal and placental metabolism for some analytes while dried blood spots collected for newborn screening reflects neonatal metabolism in a catabolic state.

Keywords: newborn screening ; biochemistry ; diabetes ; biochemical genetics ; dried blood spots

1. Introduction

Despite their rarity, inborn errors of metabolism (IEM) share commonalities with diabetes, such as insulin resistance, hyperglycemia and acidosis and target-organ damage [1][2]. Both IEM and diabetes involve derangements in the intermediates of protein, carbohydrate and lipid metabolic pathways. Analytes routinely tested for in newborn screening (NBS) for IEM, 48–72 h after birth, include many of the metabolites involved in these metabolic pathways. Some of the analytes tested for in NBS are deranged in diabetes overall [3][4][5][6][7] and diabetes in pregnancy [8][9][10][11][12][13][14][15]; however, these studies utilized cord blood. Cord blood as a sample for neonatal metabolic derangements has been shown to give false-negative results for amino acid and lipid disorders and for diagnosing maternal IEM in leucine, carnitine and vitamin-dependent pathways [16][17][18], reflecting placental/maternal metabolism for some analytes. Cord blood may, therefore, not give a complete picture of neonatal metabolic networks.

Residual deidentified dried blood spots (DBS) derived from routine NBS form a biobank and have been used in a few diabetes studies (mostly from Europe) and have given insight into the disease pathophysiology. Recent exciting publications from the Hyperglycemia and Adverse Pregnancy Outcomes study (HAPO), using cord blood [11,15], have highlighted the potential importance of intermediate metabolites in the pathophysiology of diabetes. The question arises how much of this pattern is neonatal and whether similar analyses using NBS could provide additional insights. This article will summarize the available literature on NBS and diabetes, illustrate how the results of NBS may complement cord blood-based research, provide insight on reasons behind the lack of secondary research using analyzed NBS results and make recommendations regarding future research.

2. Newborn Screening Dried Blood Spots vs. Cord Blood in Diabetes Research: Advantages and Disadvantages as a Testing Sample

2.1. Sample Volume and Storage

The small amounts of blood volume needed in newborn screening (50–75 µL per blood spot) provides an additional advantage for population-based screening: once dry, the blotted filter paper can be sent via mail from collection centers to the testing laboratory, avoiding the need for couriers. The attractiveness of using DBS has filtered from NBS to mainstream medicine, finding uses such as HbA1c monitoring, maternal research, infection diagnosis, drug monitoring, a source for DNA postmortem (identification and diagnosis) and the like [19][20][21][22][23][24].

Sample volumes of DBS limit its use in untargeted metabolomic techniques. Furthermore, variables such as patient hematocrit, temperature, humidity and storage conditions contribute to measurements of uncertainty [17]. Importantly, McDonald and colleagues have demonstrated the feasibility of a retrospective diagnosis of neonatal diabetes using stored NBS cards [25] and that elevated glucose levels may be reliably detected in various storage conditions at day five of life.

Cord blood has the advantage of greater sample volume (between 60–110 mL), allowing its use in both targeted and untargeted metabolomic techniques and include identify analytes not typically tested in NBS. Components of cord blood such as plasma may be used for analysis, without the need to test or correct for hematocrit. A controlled set temperature

of between −70 to −20 °C is necessary, but the rigid storage conditions dictated minimize measurements of uncertainty. It is possible to blot cord blood into filter paper for analysis, but the sample becomes subject to the same conditions as the DBS in NBS with similar measurements of uncertainty.

Other practical issues can also impact on the availability of collection. For example, cord blood has other clinical uses (e.g., banking for stem cell transplant), and volumes can be limited under some circumstances, while a neonatal heel prick is generally only used for IEM screening and is universally collected. NBS is now part of clinical care, so it adds no additional work burden on clinical staff, while cord blood collection remains a nonroutine endeavor unless an explicit local policy (e.g., for research purposes).

2.2. Time of Sampling

Multiple studies in NBS have demonstrated compromised sensitivity and specificity for detecting target disorders if samples are collected immediately after birth [16][17][18]. This is due to the physiologic variability of normal ranges in analytes occurring immediately after birth, during the transition from placental/maternal metabolism to neonatal metabolism. For example, thyrotropin (thyroid stimulating hormone; TSH) demonstrates a physiologic surge after birth, and results of early sampling may give a false-positive result for congenital hypothyroidism. Phenylalanine and tyrosine, reported as deranged in some studies of cord blood and GDM, also vary widely from as early as the first hour of life [9][11]. It is due to the hourly and daily variability of some of these analytes that DBS are collected typically at 48–72 h after birth, facilitating better pick-up rates for disorders of fatty oxidation. The practice in Australia is to request resampling if samples are collected too soon after birth.

Umbilical cord sampling usually takes place at birth involving the immediate collection of larger blood volumes. Paired samples of umbilical cord and maternal blood may provide information on differences between the maternal and fetal metabolome [11][15] and demonstrate the physiologic differences that surround maternal and fetoplacental metabolism. The drawback of using cord blood (or any blood sample) drawn at birth is that it may not provide accurate information on neonatal physiology that is independent of maternal influence [16][17][18].

2.3. Analytes Assessed

Testing for multiple disorders of carbohydrate, amino acid and fat metabolism is undertaken simultaneously on the same DBS in NBS. A list of target disorders and their analytes and selected studies utilizing metabolomics that have tested for similar analytes on cord blood may be found in Table 1. It is important to note that whole blood is analyzed in the DBS sample, while cord blood, depending on which method is utilized, may use whole blood or plasma. This distinction is important: not all analytes are equimolar between plasma and its cellular components. For example, carnitine and its esters are higher in concentration in red blood cells than in plasma [26]. Cord blood samples have the advantage of being able to test known (targeted) and unknown (untargeted) analytes using either whole blood or plasma. Modeling for metabolic networks can also then be undertaken.

Table 1. Selected studies with examples of analyte deranged and the corresponding disorder.

Study	Analyte Deranged	Disorder Tested on NBS
Lowe et al. (2017) [14]	**Maternal BMI: Phenylalanine (+ association) AC C3, AC C5, AC C4; Leucine/Isoleucine Cord C-peptide and BW (+association) Arginine Cord C-peptide and SSF AC C4-OH**	**PKU/Pterin defects Propionic aciduria/methylmalonic aciduria 2-methylbutyrylCoA-dehydrogenase deficiency Isobutyryl CoA-dehydrogenase deficiency Short chain dehydrogenase deficiency Multiple acyl CoA dehydrogenase deficiency Maple syrup urine disease Arginase deficiency Short chain hydroxy acyl CoA dehydrogenase deficiency**
Kadakia et al. (2018) [15]	**Cord C-peptide (−association) Tyrosine BW (+association) AC C10:1 GDM C16**	**Tyrosinemia Secondary marker for Medium Chain CoA deficiency Very long chain acyl CoA dehydrogenase deficiency**

NBS = newborn screening, BMI = body mass index, AC = acylcarnitine, C3 = proprionylcarnitine, C4 = butyrylcarnitine, C5 = tiglylcarnitine, BW = birth weight, SSF = sum of skinfold thickness, C4-OH = 3-hydroxybutyrylcarnitine, PKU = phenylketonuria, C10:1 = decenoylcarnitine, GDM = gestational diabetes mellitus and C16 = palmitoylcarnitine.

3. Conclusions

The primary purpose of NBS is, and should remain, as screening for conditions that present and require treatment early in life with serious consequences and reasonable frequency. It can be argued that screening for adult-onset disorders in an infant raises anxieties in families, and the benefit of early treatment should be balanced with raised anxieties over additional knowledge. However, there is a wealth of knowledge on physiology that can be acquired and shared across disciplines. The timing of sample collection, which is unique to NBS, provides information on neonatal metabolism with minimal maternal and placental influence during the first few days of life, when the neonate is in a catabolic state. Demystifying metabolism as simultaneous networks and working with biochemical geneticists will aid in the understanding of both common and uncommon disorders. Perhaps the best illustration of these methods in practice is the success of Robert Guthrie himself, whose tireless efforts in the face of significant opposition (his original 1961 paper describing the bacterial inhibition assay was rejected and was not published until 1963) [27] has produced a body of knowledge from which we all continue to profit. Encouraging collaborative research between subspecialties and laboratory sciences would be a good starting point, keeping in mind the dangers of early prediction for adult-onset disorders. Nevertheless, this resource has high potential for the better understanding of the molecular pathways and mechanisms underlying future health and disease.

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