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ORIGINAL ARTICLE

Home-based color card screening for biliary atresia: the first steps for implementation of a nationwide newborn screening in Germany

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Abstract

Introduction Biliary atresia is a rare neonatal disease and the most common indication for pediatric liver transplantation. Kasai portoenterostomy is the initial treatment, aiming to prevent liver transplantation. Beyond age at Kasai, few prognostic factors are known. Multiple countries have established screening methods to reduce the age at Kasai and recent analysis shows significant better outcomes for screening cohorts. In 2016, we established a decentralized stool color card screening in Lower Saxony and we present our first 2 years of experiences.

Methods In cooperation with a major German health insurance company and the Medical Association of Lower Saxony, we established the screening project, printed 120,000 color cards, and distributed them to all maternity hospitals. Program advertises were printed in newspapers and medical journals. After the first year, the project was evaluated. Thirty maternity hospitals and local practitioners were contacted via telephone, Internet, intranet, and pediatric journals.

Results One out of seventy-six maternity hospitals (1.3%) refused to participate in the screening. 30 hospitals (40%) were contacted and 93.5% of the interviewed staff reported that stool color cards were handed out regularly and discussed with the parents. Only 20% of local practitioners assessed neonatal cholestasis to be a relevant problem during daily practice, and 55% regarded a stool color card screening to be useful.

Conclusions In the second year, we extended the screening project to outpatient maternity clinics. Based on the responses of local practitioners, we regard the voluntary screening as insufficient and we have contacted the Federal Joint Committee for the initiation of a nationwide obligatory stool color card screening.

Keywords Biliary atresia · Screening · Pilot project · Lower saxony

Abbreviations

BA	Biliary atresia
BARD	Biliary atresia and related disorders
G-BA	Federal joint committee
KPE	Kasai portoenterostomy

Introduction

Rare diseases often hide behind nonspecific symptoms and systematic algorithms for diagnostics and treatment are, therefore, scarce. Especially during infancy, the differences between transient changes and relevant pathologies are challenging in the daily routine of pediatricians. Jaundice and acholic stools during the neonatal period at presentation can be a sign of benign breast milk induced jaundice, which can last for several weeks, or be the first symptom of a relevant hepatopathy. One of the most important pathologies of this second group is biliary atresia (BA), with an incidence of 1:10,000–1:20,000 in the Western hemisphere [1–3]. BA manifests within the first weeks of life and rapidly leads to an end-stage liver failure [4]. An early Kasai procedure can restore BA in 50–60% of infants; however, in the majority, jaundice reoccurs [1, 2, 4]. It is, therefore, the most common indication of liver transplantation and co-morbidities during childhood, and only 20–30% of the affected children survive

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long-term with native liver [1, 2]. While the overall survival for infants with biliary atresia has significantly improved during the last years, the waiting list mortality for pediatric liver transplantation is still up to 15% [5, 6]. An important predictive factor for the Kasai outcome is the timing of the operation, with significant better results when the procedure is performed before 60 days of age (and younger) [4, 7, 8].

The only available German data analysis by Leonhardt et al. [9] showed that the Kasai procedure in Germany is still performed too late, and the rate of primary liver transplantation and death is higher than in other European countries. The decentralized German health care system and the absence of registries for rare cholestatic disease, anticipate reliable numbers, but even a decade after the analysis by Leonhardt et al. [9], outcome evaluations at our institution show that the average age at KPE is still above 60 days.

The World Health organization (WHO) in 1968 published a guideline for the principles and practice of screenings [10]. Based on the recommendations, screenings should identify diseases with easy and rapidly applicable tests [10]. These elements were put into practice by a Japanese research group in 1994 [11]. A stool color chart was handed out to Japanese mothers at the maternity hospital, and early referral to the pediatrician was recommended when pathologic stool colors were present. Follow-up data showed that the screening program yielded significantly earlier diagnosis of BA and younger age at KPE as well as an increase in survival with native liver [11]. The stool color card program was then adopted in Taiwan, Switzerland, and several other regions [12, 13]. Previous analysis has shown that this type of home-based screening is not only effective, but also highly cost-effective [14, 15].

We, therefore in 2016, started a pilot project in Lower Saxony, a county in north-western Germany with a population of approximately 8 million and 70,000 annual births, and distributed all maternity hospitals with stool color chart cards with the instruction to hand them out to parents. The project was invented in cooperation with the local Medical Association and a statutory health insurance company. In this study, we present our first 2 years of experience with this screening program.

Methods

Project intention

The first report on the decentralized treatment of biliary atresia in Germany by Leonhardt et al. [9] concluded that currently infants are referred too late to specialized hospitals and that long-term outcomes were inferior to international results. The Federal Joint Committee regularly updates the recommendations and obligations for investigations and examinations during the neonatal period, based on the consensus of specialists in different pediatric fields. However, these specialists stay anonym and their meetings cannot be attended by non-invited physicians. We, therefore, decided to initiate a local pilot project, proving the feasibility of stool card distributions in a voluntary program. The long-term outcomes of screened infants will be then presented to the Federal Joint Committee hopefully resulting in a national, state-run screening program.

Cost calculations

We calculated the cost of the screening program for Lower Saxony using print costs of €0.03 per card (for approximately 70,000 annual births) and compared them to the minimum long-term costs of a liver transplantation, necessary medications, and regular medical consultations. The scenario of re-do liver transplantations or graft rejections with liver biopsies and intense immunosuppression were excluded. Regarding the cost-effectiveness, we furthermore relied on the reports by Masucci et al., Mogul et al., and Schreiber et al., showing the possible economic benefit of a stool color card screening [14, 16, 17]. The included Markov Model leads to the conclusion, that a passive infant stool color card distribution could include health benefits, defined as life years gained by Masucci et al. and Schreiber et al., and could be highly cost-effective [14, 17].

Project structure

In 2014, the major German health insurance companies were contacted and asked for support. One statutory health insurance company agreed to completely fund the project. In November 2016, 120,000 cards were printed and sent to 76 maternity hospitals. In the meantime, multiple articles were placed in local medical journals and a press conference was held with the local ministry for social affairs, women, families, and health [18]. In the second year, midwifes were included into the distribution network and the stool color charts were sent to outpatient maternity clinics.

Stool color card design

The Swiss Stool Color Card research group approved the adoption of their stool color images on the German Stool Card, and on the backside, a short explanation of neonatal cholestasis was present in German, English, Turkish, Arabic, and Russian.

Project evaluation

For the first evaluation, the participating maternity hospitals were stratified by annual birth rate: < 1000 births per year (group A), 1000–2000 births per year (group B), and > 2000 births per year (group C). Based on the annual birth rate, ten representative hospitals from each group were selected, due to economic reasons, and contacted and interviewed via telephone.

At the same time an evaluation was started, contacting all local practitioners via an intranet platform (PädInform®), and a survey was published in pediatric journals [19].

Results

Project participation

More than 120,000 were distributed to all inpatient and outpatient maternity clinics ($n = 76$) and only one department (1.3%) refused to participate without reasons. A local educational program was offered, but again was denied by the head of the department.

Patient identification

The Department of Pediatric Surgery at the Hannover Medical School is a nationwide referral center for biliary atresia. From all children born in Lower Saxony and referred to our center for further diagnosis because of neonatal cholestasis during the observational period, only in two cases, early admission to the hospital was based on pathologic results in the home-based stool color card screening. In the first case, diagnostics confirmed biliary atresia and the child underwent Kasai procedure at an age of 45 days. At the 1-year follow-up, this patient shows a jaundice-free survival with native liver. In total in one out of 7 children (14.3%) with BA, born in Lower Saxony during the observational period, a continuous screening with the stool color card was performed. In the other case, a child was referred to the hospital based on the results of the stool color card screening and further diagnostics confirmed an alpha-1 antitrypsin deficiency. Although all children from Lower Saxony referred to the Department of Pediatric Surgery or Gastroenterology were born in participating maternity hospitals, during consultations, parents reported that they have not received stool color cards, were not instructed in the application, or were not informed about the necessity of the screening by the hospital staff.

Program evaluation

Maternity hospitals' participation

All maternity hospitals in group A (< 1000 annual births) received stool color cards, and 80% distributed them regularly to the parents. The inconsistent distribution in the other departments was based on the voluntary character of the screening and lack of training for the nurses. In the majority of maternity hospitals in this group, parents were instructed to contact local practitioners for any questions regarding the stool color card and the card application was not explained to parents by midwifes, nurses, or gynecologists during the hospital stay. No negative feedback from parents was reported.

Equivalent results were detected for group B hospitals (1000–2000 annual births). Stool color cards were handed out regularly by 90% of the staff (midwifes and nurses), and one department did not participate in the study. In one hospital, the pediatricians offered parents an introduction in the card application. In the majority of group B hospitals, a pediatric department was included in the program and the project participation, and card distribution was obviously better than in maternity hospitals with a visiting pediatrician for the first postnatal examination.

In the group C maternity departments (> 2000 annual births), all hospitals had a pediatric department, every department participated in the project and distributed the color cards frequently, and instructed parents in the card application.

Local practitioner participation

According to the medical registry of Lower Saxony, which is organized by the Medical Association of Lower Saxony, 718 pediatricians (hospital staff and practitioners) work in Lower Saxony. Despite recurring appeals in multiple pediatric journals as well as the intranet of local practitioners, only 20 (2.8%) agreed to participate in the evaluation. No additional participants joined after the deadline was extended. Only four (20%) of the contacted practitioners regarded neonatal cholestasis to be a relevant problem in their daily routines with newborns, and nine local practitioners (45%) doubted the positive effect of the stool color cards.

Discussion

In 2011, the BA research group at the Hannover Medical School started the first evaluation of BA treatment in Germany to create a representative image of care. Results were

sobering—too many centers were treating this rare disease, and the number of primary liver transplantations was higher than in other European registries [9]. During the 2014 International Congress on Biliary Atresia and Related Disorders (BARD) in Berlin, various centers discussed that the stool color card screening improved BA outcomes across several metrics, including survival with native liver following Kasai procedure [11–13]. More specifically, the screening led to an earlier referral to specialized centers, and then to a younger age at KPE—the most important prognostic factor [7, 20, 21].

In Germany, no comparable program for early detection of neonatal cholestasis was established, but the Joint Federal Committee (G-BA) mandated a stool color control during early medical checkups [22]. These stool color control are necessary but not sufficient; because of the wide time range of checkup consultations, jaundice patients continued to be referred to pediatric gastroenterologists too late due to delayed presentations to local practitioners. Home-based stool screenings, as implemented recently in Japan, Taiwan, and Switzerland, are more effective, because they include the parents into the screening process [11–13]. Recently, the analysis by Witt et al. from the Netherlands showed that when color cards were applied, the sensitivity of the stool color evaluation by parents increased from 66 to 87% [23, 24].

Therefore, stool color cards need to be handed out to patients as soon as possible—in the maternity hospitals. Our first evaluation showed that medical staff at the birth clinics were appropriately cooperative, with frequent use of the cards in 93.5% of the departments on a voluntary basis. The analysis further showed that departments with high annual birth rates, which generally have an integrated pediatric department, participate at higher rates, and support the screening program without exception. However, during our observational period, only one of the seven regional BA cases was identified early by parents using the stool color card. In all other cases, parents did not receive stool cards or were not informed about the necessity of the continuous screening by the hospital staff at the maternity hospital. This is another parameter for evaluating the voluntary character of the pilot project. Furthermore, we do not know if any infants were referred to centers outside of Lower Saxony due to the decentralized care in Germany. We can only improve the lack of necessary information with a centralization of rare diseases and obligatory registries (Figs. 1, 2).

The lack of collaboration from local practitioners was sobering. Despite multiple appeals, only 20 local practitioners participated in the evaluation of the pilot project, and the majority provided negative feedback. While all pediatric staff at birth clinics regarded neonatal cholestasis as a relevant problem in their daily routines, only 20% of local practitioners answered the same. Therefore, we doubt that this number is representative and we assume that the majority tacitly supports the project, like their representatives in the Medical Association of Lower Saxony. Neonatal cholestasis is clearly underestimated in the daily routine [25–27]. Not infrequently, neonates are referred to the hospital with major complications such as intracranial bleeding due to vitamin deficiency and synthesis problems for clotting factors [28, 29].

Despite the current efforts, the success of the stool color card screening cannot be measured based on patient cohorts from Lower Saxony alone. Given the current estimations of 70,000 annual births in this region, we expect 3–4 BA cases per year. Therefore, the program needs to be extended nationwide and the study should include comparisons to a pre-screening cohort, which is a difficult task in a decentralized health care system. The only

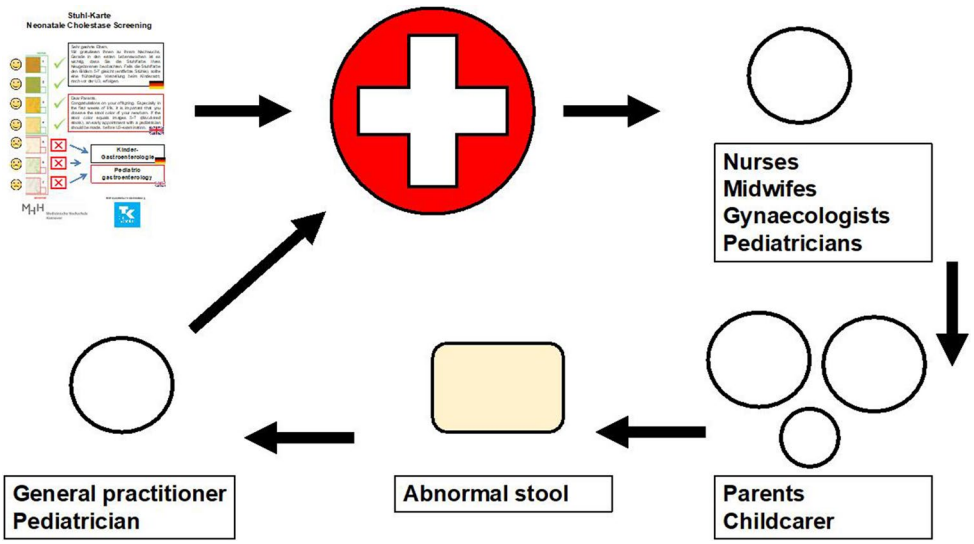

Fig. 1 Distribution pathway of the stool color cards. Based on the annual birth numbers, stool color cards were distributed to all maternity hospitals with instructions for nurses, midwifes, gynaecologists, and pediatricians—the cards were handed out to the parents, with the recommendation for daily controls of the stool color within the first weeks of life of the newborn. When abnormal stool colors were detected, an early appointment with the local practitioner was advised and, if necessary, a referral to a pediatric gastroenterology department

Fig. 2 Stool color card in Lower Saxony. The stool color card includes a color chart from 1 to 7 (5–7 pathological results) and corresponding pictograms. The backside of the card includes information on neonatal cholestasis in five languages (German, English, Turkish, Russian, and Arabic), based on the current population distribution in Germany

comparable German analysis, by Leonhardt et al., is more than 10 years old, and we are the first to work on a reevaluation [9].

Another limitation is the voluntary character of the pilot project—despite the fact, that all pediatricians and gynaecologists working at the participating hospitals supported the project, the cards were distributed by nurses and midwifes, who did not feel obligated to participate and some demanded a special training in the card application. To continue an effective program, therefore, a compulsory screening with a nationwide education campaign is necessary.

In the United States, another local screening for neonatal cholestasis was started, with recurrent blood sampling of liver function tests [30]. Sensitivity and specificity are significantly better than the stool color card screening, but include recurrent traumatization for the infants.

In a recent analysis, the authors in Goodhue et al. [31] concluded that a screening program for BA even in countries with a low incidence is beneficial. We agree with this theory and are in turn supported by multiple pediatric gastroenterologists and hepatologists. We have recently extended our local program to outpatient maternity clinics in Lower Saxony. We have contacted the Federal Joint Committee (G-BA) for approval of a nationwide screening program, and we continue to await a decision.

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Compliance with ethical standards

Conflict of interest None of the authors have a conflict of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

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