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Acute neonatal bilirubin encephalopathy in the State of Utah 2009–2018

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ABSTRACT

Herein we report a case series of seven newborn infants, all apparently well at birth, who in the period since 2009 were cared for in the State of Utah with acute bilirubin encephalopathy (ABE). This report summarizes our attempts to define common features of these seven through a state-wide voluntary registry, as a step toward devising new means of preventing such cases in the future. In previous reports of ABE, many of the affected neonates had no clearly defined explanation for their progressive hyperbilirubinemia. Our efforts to identify clear explanations in all seven cases included next generation DNA sequencing, testing a panel of 28 genes involved in bilirubin production and metabolism. We found that *hemolytic disease* was a unifying feature of these seven; two had DAT (+) Anti-D or anti-c hemolysis, while five had confirmed mutations in genes involved in bilirubin production and or metabolism that were previously unrecognized in these families.

1. Introduction

In 2009 Drs. Lois Johnson and Vinod Bhutani reported findings from the Pilot USA Kernicterus Registry [1,2]. During the 13-year period 1992 to 2004, infants cared for in US healthcare facilities were voluntarily reported to this registry. One-hundred-twenty-five neonates met eligibility criteria for ABE or post-icteric sequelae, and were the subjects of the reports [1,2]. Among the findings, 69 of the 125 (55.2%) had no clear explanation for the extreme hyperbilirubinemia and were therefore termed "idiopathic". These neonates were mostly breast but with signs of sub-optimal intake and dehydration. Of those with a recognized genetic etiology, glucose 6 phosphate dehydrogenase (G6PD) deficiency was identified in 26 (20.8%), and hereditary spherocytosis (HS) in three (2.4%).

Following those reports, we published somewhat similar findings from the Intermountain Healthcare hospitals. Intermountain Healthcare incudes a group of 22 not-for-profit hospitals with labor and delivery services located in Utah and Idaho [3]. Of 32 neonates in our database with a total serum bilirubin (TSB) > 30 mg/dL, an etiology for the hyperbilirubinemia was recognized in only 11. Of these, two had G6PD deficiency and four had DAT (+) hemolytic disease. Thus 21 (65.6%) were termed "idiopathic" hyperbilirubinemia. Moreover among 113 neonates who had a highest recorded TSB in the range from 25 to 30 mg/dL, 85 (75.9%) had no etiology recognized for their extreme hyperbilirubinemia [3].

Based on those findings, we hypothesized that physicians caring for neonates with hazardous (TSB > 30 mg/dL) or extreme (TSB 25–30 mg/dL) hyperbilirubinemia can be so focused on decreasing the TSB to safe levels that they often do not rigorously attempt to discover why the bilirubin level became so elevated in the first place [3]. This speculation stimulated us to devise a next generation sequencing (NGS) panel to search for genetic causes of hazardous or extreme neonatal hyperbilirubinemia, particularly when the family history and simple testing for causation (such as DAT testing and G6PD enzyme levels) were unrevealing [4]. We postulated that discovering underlying genetic causes, and not being satisfied with terming the condition "idiopathic", would have value to physicians, families, and society. Specifically, we reasoned that determining an etiology would provide clarity to healthcare workers and families, and might generate information relevant to management and prevention of hyperbilirubinemia in future pregnancies in those families.

The present case series reports our attempts to identify the cause of each patient when a newborn infant was treated for acute encephalopathy associated with severe hyperbilirubinemia in any hospital in the State of Utah since our NGS hemolytic panel became available,

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Table 1
Live births in Utah January 2009 through April 2018, accessed from Utah's Vital Statistics.

	2009	2010	2011	2012	2013	2014	2015	2016	2017[a]	2018[a]	Total[a]
Live births	53,849	52,146	51,144	51,439	50,913	51,164	50,776	50,486	50,000	16,600	428,031
ABE cases	1	0	0	1	1	1	0	1	1	1	7

ABE, acute bilirubin encephalopathy.
[a] Estimate (actual count not yet available).

Table 2
Seven cases of acute bilirubin encephalopathy treated in Utah hospitals January 2009 through April 2018.

Year	Highest TSB (mg/dL)	DOL highest TSB	GA (wk/day) at birth	Mother's blood group	Neonate's blood group	DAT	Conditions discovered
2009	38.0	9	38 5/7	A+	O+	−	PK deficiency, 1529A
2012	41.7	6	37 2/7	O+	B+	−	HS, Band 3 mutation E508K
2013	41.0	5	40/0/7	O+	B+	−	G6PD deficiency (Mahidol) 478A
2014	41.9	5	38 4/7	O+	O+	−	G6PD deficiency (African) 202A and 376G, plus Gilberts (TA)7
2016	29.2	2	39 3/7	O+	A+	+	Anti-c (1:256)
2017	44.3	6	38 2/7	B+	B−	−	HS, mutations in Band 3 E40K and beta spectrin S1763G
2018	28.5	4	35 1/7	O−	O+	+	Anti-D and Anti-c

TSB, total serum bilirubin; DOL, day of life; GA, gestational age; DAT, direct antiglobulin test; PK, pyruvate kinase; HS, hereditary spherocytosis; G6PD, glucose 6 phosphate dehydrogenase.

2. Case series and methods

During the period 1/1/2009 through 4/30/2018, approximately 428,031 live births were recorded in the State of Utah (Table 1). During this same period, seven newborn infants were cared for in Utah hospitals with a diagnosis of acute bilirubin encephalopathy [5], giving an estimated incidence of 1 case per 61,147 live births (1.6 ABE events per 100,000 live births).

As shown in Table 2, the highest recorded TSB in these seven was 44.3 mg/dL (the patient born in 2017) and the lowest of the peak values was 28.5 mg/dL (the patient born in 2018). The two neonates where the highest recorded TSBs were in the high 20's both had DAT (+) isoimmune hemolytic disease with the highest recorded TSB in the first days after birth. The latest peak TSB recorded was nine days after birth (2009). Gestational age of the seven neonates ranged from 35 1/7 (2018) to 40 0/7 weeks (2013). Two had DAT (+) hemolytic disease (2016 and 2018) and the other five each had a genetic condition discovered as part of their evaluation for hyperbilirubinemia. All seven underwent exchange transfusions preceding and followed by intensive phototherapy for their peak TSB. The genetic conditions and the exact mutations discovered are shown in the last column of Table 2.

Table 3 lists the criteria by which these seven were judged to have mild, moderate, or severe ABE. Before their exchange transfusions, all had periods of hypotonia and/or obtundation. Five also had periods of opsthotonic posturing with a high-pitched cry. Three had seizures and all seven had periods of apnea. Five had brainstem auditory evoked response (BAER) testing within one week after the exchange transfusion. All failed the test and audiology deemed the failures to be in keeping with the diagnosis of bilirubin oto-neurological impairment. Only three of the seven had an MRI within one week after the exchange transfusion and no evidence of kernicterus was identified. Follow-up included one early death, and three with little or no follow-up information because they have either moved from the state or are cared for outside the University of Utah or Intermountain Healthcare medical records systems. Early neonatal death of the patient born in 2013 was reported previously as an example of presumed sepsis that was actually kernicterus (pathologically proven) [6]. The patient in 2012 with hereditary spherocytosis with a Band 3 mutation was also published previously as an example of a case of "idiopathic" acute kernicterus that was later found to have HS with a recognized mutation [7].

Two of the seven were born at home by intention (2009 and 2017) (Table 4), and were taken by parents or grandparents to a hospital emergency department on day 9 (2009) or day 6 (2017) with extreme jaundice. The other five were all born in a hospital. Those five all had a TSB measured in the birth hospital; in two, the first measured TSB was in the "critical risk" zone (> 99th%). These were both cared for in a well baby nursery. One (2016) was immediately transferred to the neonatal intensive care unit (NICU) for exchange transfusion and continued management. The other (2018) was treated with phototherapy in the well baby nursery, then discharged home with instructions to return for a bilirubin check 24 h after discharge. That repeat TSB was 28.5 mg/dL and the patient was hypotonic and apneic in the emergency department and was admitted to the NICU for exchange transfusion and continued management. Two of the neonates (2012 and 2013) had a TSB in the birth hospital that fell within the "high risk" zone (> 95th %), and one (2014) within the "high intermediate risk" zone. These three were treated with phototherapy in the birth hospital, then discharged with instructions to return for a repeat TSB measurement, and phototherapy if indicted, within 24 h (2012) or within 72 h (2013 and 2014), at which time the TSB values were 41.7, 41.0, and 41.9 mg/dL respectively.

NGS was performed on blood samples received by the Associated Regional and University Pathologists (ARUP) Laboratories as part of the clinical work-up for extreme hyperbilirubinemia. Our methods have been published previously [4,8,9]. The current diagnostic panel includes 28 genes encoding cytoskeletal proteins and enzymes, and genes involved in bilirubin uptake and conjugation, covers the complete coding region, splice site junctions, and, where appropriate, deep intronic or regulatory regions. Targeted gene capture and library construction for next-generation sequencing (NGS) are performed using Sure Select kit (Agilent Technologies, Santa Clara, USA). Prior to sequencing on the Illumina Next Seq (Illumina Inc., San Diego, CA) instrument, indexed samples are quantified using qPCR and then pooled. Samples are sequenced using 2 × 150 paired end sequencing.

3. Discussion

Successful programs to reduce future cases of bilirubin damage could be informed by more clearly understanding the pathogenesis of past and present cases. However, in attempting to use our present case