Infant botulism in Denmark from 1995 to 2015

Bergitte Drivenes[1], Tyra Grove Krause[2], Mikael Andersson[3], Luise Müller[2], Kurt Fuursted[4], Tanja Pedersen[5], Anne Kirkeby Hansen[5] & Malene Landbo Børresen[1]

ABSTRACT

INTRODUCTION: Infant botulism is a rare, probably underdiagnosed, life-threatening disease caused by the toxin-producing bacterium *Clostridium botulinum*.

METHODS: We investigated reported cases of infant botulism in Denmark from 1995 to 2015, and compared the incidence with that of other western countries.

RESULTS: We found nine cases of infant botulism in Denmark from 1995 to 2015. The incidence of infant botulism in Denmark was similar to that seen in other western countries, but likely underestimated. The source of infection was only confirmed in a single case. Four cases received botulism immune globulin, intravenous (BIG-IV), which was administered within 7-10 days from admission.

CONCLUSIONS: Infant botulism is probably underdiagnosed. Increased awareness is crucial to be able to recognise the condition. The time delay from hospital admission to administration of BIG-IV is challenging. Studies have shown that BIG-IV reduces both mean duration of intensive care and mean length of hospital stay; however, this was not confirmed in our work due to the limited number of patients.

FUNDING: none.

TRIAL REGISTRATION: not relevant.

Botulism is a rare, potentially life-threatening neuroparalytic disorder caused by neurotoxins produced by the gram-positive, anaerobic, spore-forming bacterium *Clostridium botulinum*. The bacterium is present in environments with soil and aquatic sediment [1]. Botulism can be divided into three clinical groups; infant botulism, foodborne botulism and wound botulism. Moreover, eight different toxin types (named A-H) have been identified. However, only toxins A, B, E, F and H are known to cause disease in humans. Infant botulism is primarily caused by neurotoxins A and B, and occurs in infants up to 12 months of age, most commonly from six weeks to six months of age. It is caused by ingestion of spores from *C. botulinum*. The bacteria colonise in the gut due to the immature gut flora. A release of neurotoxins into the bloodstream follows. An irreversible binding of neurotoxins to receptors on presynaptic nerve endings causes a blockade of the acetylcholine release. The clinical presentation of infant botulism can vary from unspecific symptoms to a fulminant flaccid paralysis and need of long-term hospitalisation with high-intensive care. Most commonly described are symptoms like poor food intake, constipation, reduced facial mimics, ptosis, diminished pharyngeal reflexes and hypotonia. Patients are usually afebrile with unaffected consciousness and sensory system. Infant botulism can mimic a broad spectrum of medical conditions and diseases including sepsis, dehydration, neuromuscular disorders, Guillan-Barré syndrome, myasthenia gravis and encephalitis, just to mention a few [1-7].

The diagnosis of infant botulism is confirmed by laboratory findings. Earlier, mouse-neutralisation bioassay was, and in some laboratories in Europe is still considered the gold standard. This method is based on injection of patient serum into mice. If the injection sample contains toxin, the mice will typically develop signs of botulism within a few days. The toxin type is determined by neutralisation of the toxin with specific antitoxins. Mice treated with the neutralising antitoxin will survive, while the untreated mice will develop botulism. In parallel to this, the growth of *C. botulinum* in a stool sample is also investigated. Since the early 2000s, a polymerase chain reaction (PCR) method with high sensitivity for the detection and determination of the toxin type in the stool has been available, reducing turnover time to diagnosis to less than 24 hours [2, 4, 8].

In Denmark, botulism has been a notifiable disease since 1983. However, no systematic review of the notified and diagnosed cases of botulism in Denmark exists [9-11]. A "cluster" counting three notified cases was seen in Denmark from December 2014 to March 2015, this has not previously been published. We made an inventory of cases in Denmark to investigate whether this pattern was unusual.

The aim was to identify cases of infant botulism from 1983 to 2015 in Denmark, using all possible data sources, and to compare the incidence rates (IR) with those of other countries. Furthermore, we aimed to describe the source of infection, laboratory diagnosis, the clinical course including treatment with antitoxin, and the outcome.

METHODS

The Civil Registration System includes all persons who have lived in Denmark since 2 April 1968 [12]. All such residents have been assigned a unique personal identification number, which allows linkage across Danish na-

ORIGINAL ARTICLE

1) Department of Paediatrics, Amager and Hvidovre Hospital
2) Department of Infectious Disease Epidemiology, Statens Serum Institut
3) Department of Epidemiology Research, Statens Serum Institut
4) Department of Microbiology and Infection Control, Statens Serum Institut
5) Department of Paediatrics, Aarhus University Hospital, Denmark

Dan Med J 2017;64(9):A5404

TABLE 1

Incidence rates of infant botulism in Denmark compared with the five countries worldwide with the highest number of cases of infant botulism.

Country	Time period	Cases, n	Births, n	IR/100,000 (95% CI)
USA	1976-2006	2.419	119,420,626	2.03 (1.95-2.11)
Argentina[a]	1982-2006	410	17,025,837	2.41 (2.19-2.65)
Australia	1978-2006	32	7,197,790	0.44 (0.31-0.63)
Italy	1984-2008	29	13,771,186	0.21 (0.15-0.30)
Canada	1979-2006	27	10,134,090	0.27 (0.18-0.39)
Denmark				
	1995-2006	2	791,408	0.25 (0.06-1.01)
	2007-2015	7	543,333	1.29 (0.61-2.70)
	1995-2015	9	1,334,741	0.67 (0.35-1.30)

CI = confidence interval; IR = incidence rate.
a) No number for annual live births was found for 1984 and 1986, and these values are calculated as averages from 1983 and 1985, and from 1985 and 1987, respectively.
Sources: [2], http://data.un.org/Data.aspx?q=live+births&d=POP&f=tableCode%3a62, https://unstats.un.org/unsd/demographic/products/dyb/dyb2.htm, www.statistikbanken.dk/statbank5a/SelectVarVal/Define.asp?MainTable=FODDAG& PLanguage=0&PXSId=0&wsid=cftree (17 Mar 2017).

ABBREVIATIONS

BIG-IV = botulism immune globulin, intravenous
DHA = Danish Health Authority
DNPR = Danish National Patient Registry
IR = incidence rate
PCR = polymerase chain reaction
SSI = Statens Serum Institut

tional registers. Statens Serum Institut (SSI) is the national diagnostic reference laboratory for botulism. Botulism has been clinically notifiable since 1983 [13], and suspected cases should be reported to the Danish Health Authority (DHA) and SSI immediately. From SSI as well as from the DHA we received extracts of all laboratory confirmed and notified cases of infant botulism in Denmark since 1983.

The Danish National Patient Registry (DNPR) is a nationwide register of all hospital discharge diagnoses made from 1 January 1977 to the present [14]. Since 1 January 1994 it has been based on the International Classification of Diseases, tenth version (ICD-10) classification. We extracted from the DNPR on botulism (DA051), then we restricted the data to children below 12 months of age to include only cases of infant botulism.

The IR was estimated as the number of events divided by the number of live births (in 100,000s) in the observed periods. All estimations were made using SAS Genmod Procedure in SAS version 9.4 (Cary, NC).

Trial registration: not relevant.

RESULTS

We found nine confirmed cases of infant botulism in Denmark from 1995 to 2015 in the database of DHA/SSI. All nine cases were also found in the DNPR. No cases were notified to the SSI/DHA before 1995. Four more cases of infant botulism were registered in the DNPR; however, these cases were not registered in the database of SSI or the DHA and thus could not be confirmed as infant botulism in the DNPR. These four cases were therefore excluded. Hence, nine cases of infant botulism in Denmark from the 20-year period were included in the analyses with three cases in 2012 and 2015, respectively. The IR in Denmark for infant botulism from 2007 to 2015 was 1.29 (confidence interval: 0.61-2.70). This number is almost five times higher than the IR for 1995-2006, and two times higher than the overall incidence for the 1995-2015 period, respectively (**Table 1**).

There was a predominance of female patients with eight girls and only one boy. All nine patients were 1-6 months of age. An uneven geographic occurrence of cases was seen as only three out of the five Danish healthcare regions were represented (Capital Region of Denmark, Central Denmark Region and North Denmark Region, respectively).

All patients went through an investigation programme comprising at least one of the three mentioned tests for infant botulism. Five out of the nine patients tested positive for toxin B, three out of nine patients tested positive for toxin A, and three patients tested positive for more than one toxin; A and B, B and F, and A and E, respectively.

The source of infection was confirmed only in one of the nine patients. C. botulinum was identified in a jar of honey from the honey batch that the patient had consumed [11]. For the remaining eight patients, the source of infection was either unknown, or test results from the suspected baby porridges tested negative for C. botulinum.

Four of the nine patients were treated with the human derived antitoxin received botulism immune globulin, intravenous (BIG-IV) (also called BabyBIG), and with conservative treatment. The time from hospital admission until treatment with BIG-IV was 7-10 days. Three out of nine patients suffered from respiratory insufficiency and were ventilated mechanically. The median length of hospitalisation was 33 days (range: 13-76 days), and the median length of follow up in the outpatient clinic was 36 days (range: 13-389 days).

At discharge, one patient was reported to have neurogenic bladder dysfunction and needed intermittent catheterisation twice a day for a total period of ten months. Six of the nine patients were reported to be either free of sequelae or to have mild sequelae; however, no treatment was required. For the remaining two patients, information about their clinical condition at the time of discharge was not provided. No patients died.

DISCUSSION

We made a nationwide survey of all reported cases of infant botulism in Denmark, following the first Danish case of infant botulism described in 1995. From 1995 to 2015, only nine cases were registered corresponding to an annual incidence of 0.67 (Table 1). Worldwide, the USA has the highest number of reported and identified cases of infant botulism. In 2014, a total of 128 laboratory-confirmed new cases were reported in the USA a country with a birth cohort of 3,998,175 children, corresponding to an IR of 3.2 [15]. However, over a period of 30 years (1976-2006) the estimated IR was 2.03 (Table 1). As seen in Table 1, the overall IR in Denmark is comparable with the rates in other western countries except for the USA and Argentina [2, 16].

Several studies suggest that infant botulism is both under-recognised and under-reported [2, 16, 17]. Lack of awareness of the disease is a possible explanation. The unspecific clinical course makes diagnosis difficult [1-3]. Furthermore, in Denmark, under-reporting must be suspected, both due to the very few cases recorded over the 20-year study period, and since all Danish cases of infant botulism were reported from only three of the five Danish healthcare regions. Furthermore, the clustering of reported cases seen in Denmark the recent years might reflect a short-lived increased awareness of the diagnosis among paediatricians following a recent case.

Consumption of honey is considered a well-known risk factor for infant botulism. Canned baby food, porridge and soil are also potential sources of infection [1, 4, 18, 19]. However, it is difficult to establish the source of infection, and our finding of only one confirmed source of infection in the nine patients is in line with reports from other studies [1]. Based on the limited clinical information in our case series, we cannot draw any conclusion about the relation between toxin type and number of toxins, and the severity and sequelae. However, several studies claim that a more rapid and severe course of disease is correlated to type A toxin botulism [1, 2].

Clinical progression of infant botulism can be prevented by antitoxin. In 2003, BIG-IV was licensed in the USA for treatment of infant botulism, and since 2005 BIG-IV has also been available for the treatment of infant botulism outside of the USA [2, 20]. In Denmark, BIG-IV is not on stock, but can be ordered from the USA on a case-by-case basis.

Studies have shown that treatment with BIG-IV reduces both the mean duration of intensive care and the mean length of hospital stay [1, 7, 20]. Of the nine cases of infant botulism observed in Denmark from 1995 to 2015, only four received BIG-IV treatment. There were several days of delay from admission to administration of BIG-IV due to diagnostic delay and time needed for import of BIG-IV from the USA.

Prompt treatment with BIG-IV is recommended, even if test results are not yet available [1]. With the remarkably improved turnover time for test results, it might be discussed whether it would be acceptable to wait for PCR results before giving BIG-IV. Furthermore, access to a common European stock of BIG-IV would reduce the delay from diagnosis to administration of BIG-IV. Supportive conservative treatment, however, is essential. Patients with mild disease courses have shown an ability to recovery fully without BIG-IV treatment.

CONCLUSIONS

We found that the IR of infant botulism was lower in Denmark than in the USA; however, the IR varied considerably in Denmark. This could partly be explained by underdiagnosing. Hence, increased awareness of the unspecific symptoms of the disease and relevant diagnostic tests is needed to identify infant botulism and initiate timely treatment.

CORRESPONDENCE: *Bergitte Drivenes.* E-mail: bergittedrivenes@gmail.com
ACCEPTED: 12 July 2017
CONFLICTS OF INTEREST: Disclosure forms provided by the authors are available with the full text of this article at www.danmedj.dk

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