Neonatal jaundice – what’s new?

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Norway

• Facts
  – Pop. ~5 million
  – Births: 58,000/yr
  – Neonat mortality: 2.4/1000
  – Infant mortality: 3.4/1000
  – Prematurity rate: 8.5%

Norway

• 21 pediatric departm.
  – 7 in university or university-affiliated hospitals
  – 3 of which in “greater Oslo”
• “SOMETHING OLD, SOMETHING NEW, SOMETHING BORROWED, SOMETHING BLUE”
  – As for wedding apparel – so also for lectures about neonatal jaundice
    • Much knowledge about neonatal jaundice is old
    – and some of this knowledge has its roots in Latin America!
    • But we have learnt something new in recent years
    • And yes, I have borrowed a couple of the illustrations for this lecture
    • The blue is for the favorite color of phototherapy lights
  – as well as the theme color for these slides
• Jaundice is the most common cause for diagnostic works-up and therapeutic intervention in neonates
• Virtually all newborns have "biochemical jaundice"
• Visible jaundice requires total serum bilirubin (TSB) levels of >80-100 μM/L (5-6 mg/dL)
  – The incidence of TSB >200 μM/L may vary from 6 - >30%, depending on a multitude of factors
• Bilirubin and the brain
  - We worry about jaundiced newborns because bilirubin can get into the brain
  - In rare instances babies may end up looking like this:

Neonatal jaundice

And if they survive, this is what their lives may be like:

Neonatal jaundice
Neonatal jaundice

• “Something old…”
  – Neonatal jaundice may have been described in a Chinese textbook >1000 years ago
    • The oldest text in my personal collection is from 1473 – Bartholomeaus Metling: Ein Regiment der jungen Kinder.
      • Metling believed that jaundice in suckling infants was due to thick milk which caused congestion of the bile ducts
  – French medical texts from the 17-1800s contain quite a few studies and theses on neonatal jaundice
    • The suggested treatments ranged from the harmless
      – but probably ineffective
    – to outright dangerous
      – and still probably ineffective
  – Bilirubin was first described in 1827 by the French chemist Baron Thenard

Neonatal jaundice

• “Something old…”
  – German medical textbooks during the last half of the 1800s moved from
    • Recommending treating neonatal jaundice with lukewarm baths and enemas
      – to state that no treatment was necessary, and
      – that the currently available treatments were of no value
    • And from believing that the problem was localized to the liver
      – to increasingly recognize the central role of red cell breakdown and increased bile pigment production

Neonatal jaundice

• “Something old…”
  – Kernicterus was first described in the the German pathologist Johannes Orth in 1875
  – But described in detail by Christian Georg Somoli in 1904
Neonatal jaundice

• "Something old…"
  – The first description of a case series of Rhesus isoimmunization has been ascribed to JA Arkwright
    • 1902 – Edinburgh Medical Journal
  – But he may in fact have been preceded by almost a century by the French ex-naval surgeon Louis Sylvestre Beraud
    • "Observation sur l’ictère congénital", University of Montpellier, France, 1817

Neonatal jaundice

• Real treatment
  – The first successful exchange transfusion was described by Hart
    • Can Med Assoc J 1925
    – The infant survived, though the Rhesus blood group system wouldn’t be discovered for more than a decade
    – Probably for this reason, further attempts to exchange were not reported until the 1940s
  – Exchanges were then increasingly used in the 1950s, using a push-pull technique through the umbilical vein

Neonatal jaundice

• Real treatment
  – “Sister J. Ward, the sister in-charge of the Premature Unit (chosen because of her known skill in rearing puppies) was a keen fresh air outdoor fan, and on warm summer days would wheel the more delicate infants out into the courtyard, sincerely convinced that the combination of fresh air and warm sunshine would do them much more good than the stuffy overheated atmosphere of an incubator.”
    – Dobbs RH & Cremer RJ, 1975
Hallowed phototherapy grounds:
Rochford General Hospital
Southend-on-Sea

Spreading the word
The Lancet 1958

The equipment and the effects
I find here a figure with the relevant data is really easier to see for the audience.

Annie; 17.04.2010
But does all the world read Lancet?

**PREVENTION OF HYPERBILIRUBINEMIA OF PREMATURITY BY PHOTOTHERAPY**

Jerald Levy, M.D., Maria Ferreira, M.D., and Jean Hewitt, A.B. *

Department of Pediatrics, University of Vermont College of Medicine, Burlington, Vermont

- Several groups of English, South American, French, and Italian workers have since reported very favorable experiences with this method of treatment.
- This therapy has not found acceptance in the United States. This is probably due to doubts as to its effectiveness and concern that the photodecomposition products might be toxic, combined with unawareness of the many reports in the foreign literature.

Pediatrics 1968

They certainly did in Brazil!

- 6 publications in 1960!*  
  - *Ana Brasileiros de Ginecologia 49:147-8
  - 19 newborn infants, mean Wt 3315 G (range 2600-4320)
  - Mean TSB 24.4 mg/dL (range 19.2-32.6)
  - ABO incompatibility 9 cases, Rh-incompatibility 3 cases
  - Mean reduction in TSB 6.5 mg/dL per 24 h (range 1.7-11.6)
    - Alternating 6 h light with 2 h darkness

The equipment

*Double publications appear to have been permitted
Recognizing the Brazilian contribution

• "In Brazil, in December 1959, Ferreira, Berezin, Barbieri, and the technician Larrubia, from the "Casa Maternal e da Infância da Legião Brasileira de Assistência de São Paulo" presented at the local medical association the results of their first experiments at that Maternity with a device developed by Ferreira and based on the description and designs by Cremer, et al.
• In this paper ….. the authors reported their clinical experience with 19 icteric newborn infants ….."
  - Senna JO, Letter to Pediatrics 46(4):644-6, 1970

Recognizing the Brazilian contribution

• "This publication was followed by a longer one whose authors Ferreira, Cardim, and Mellone analyzed the penetration of light…..
• The word phototherapy, in relation to icterus, was used for the first time in that report.
  - which was granted the most important Brazilian Pediatric Award in 1960"
  - Senna JO, Letter to Pediatrics 46(4):644-6, 1970

Slower in Norway ……..

• The (allegedly) first phototherapy "contraption" in Norway
  - Haukeland University Hospital around 1970
• A different take on "double phototherapy"?
Neonatal jaundice

• Enough history – where are we in 2012?
  – We have two well-established treatments
    • Exchange transfusion and phototherapy
  – There is one treatment about which there is still varying results and opinions
    • IVIG for Rhesus and AB0 isomunization
  – A new treatment “on the horizon”
    • Metal meso- and protoporphyrins
      – These drugs have not yet been licensed for regular clinical use
        » Long-term effects of whole-sale inhibition of heme oxygenase, even if temporary
        » Excretion of heme is accompanied by loss of iron
        » Is bilirubin “good for you”?

Neonatal jaundice

• However, the guidelines for when to intervene with treatment have a weak evidence base
  » (“Expert opinion” = “BOGSAT”)
  • (Partly) therefore guidelines vary both between and within countries
    – Some countries have national guidelines
    – In other countries two NICUs in the same city may practice different guidelines
      » or even two doctors in the same NICU

Neonatal jaundice

Examples of guidelines

AAP 2004

Norway 2006

Bilirubin values in mg/dl

Bilirubin values in mg/dl
Neonatal jaundice Guidelines

• Important questions
  – Are the guidelines founded in biology?
    • Only partially
      – The basis for most current guidelines are (limited) patient data from the 1950s and '60s
        » They are from the age of exchange transfusions
        » Many of the babies had Rhesus isoimmunization
        » Jaundice from hemolysis may carry greater risk than non-hemolytic jaundice
        » Though we really don’t know why!
  – The population basis for current guidelines is not ethnically or nationally heterogeneous
    » Therefore their portability is questionable
    » Yet AAP guidelines are used in many countries which are quite different from the USA
  – Can’t we do some big trials and find the right levels?
    • Unfortunately not, because....
      1) the only measurable endpoint is kernicterus
        » i.e. brain damage
      2) the levels are likely to vary between individuals
        » Genetic/hereditary/ethnic risk
      3) the levels are likely to vary within the same individual
        » Sick infants tolerate less
        » Acidosis, hypercarbia, sepsis, hyperosmolality
  – Many infants reported to have developed kernicterus in recent years had been discharged home
  – Guidelines must therefore also be about discharge planning and follow-up safety
    • Individualized assessment is necessary
Neonatal jaundice
Our therapies
• Exchange transfusion
  – Used to be routine
    • Every pediatric resident got her/his chance to do it – and many times!
  – Now it is rare
    • Residents routinely graduate from our program without even having seen an exchange transfusion
    – Much less performed one themselves
    • Exchange transfusions are becoming dangerous
      – Lack of practice makes any procedure risky!

Neonatal jaundice
Our therapies
• Intravenous immune globuline (IVIG)
  – Since we introduced IVIG for Rhesus and AB0 immunization in our NICU
    • The number of exchanges has dropped to 0-2 per year
    – But some report no effect of IVIG! Why?
      • There is no data to explain this disparity
        – Speculations/guesses:
          » Differences in IVIG specificity?
          » Differences in biology??
          » Differences in procedures??

Neonatal jaundice
Our therapies
• Phototherapy
  – New lights
    • Gallium nitride LEDs
      – High irradiance
        » Which can be adjusted
      – Virtually no heat production
      – But so far no evidence that they work better than fluorescent lights
        » as far as reducing TSB
Neonatal jaundice

Our therapies

• Phototherapy
  – Is there a "double effect"?
    • Effect 1: Reducing TSB by facilitating excretion of unconjugated bilirubin in bile and urine
      – This is what we have always looked for and measured!
    • Effect 2: Protecting the brain by converting 20-25% of circulating bilirubin to water soluble photoisomers
      – Bilirubin gets into brain as the predominant IXα (z,z) lipophilic isomer
      – Theoretically/hypothetically water soluble photoisomers should not cross the blood-brain barrier
        » This may well be true, but so far we have not been able to generate any experimental evidence for this hypothesis
        » But we keep trying!

Neonatal jaundice

Our therapies

• Phototherapy
  – Can phototherapy be harmful?
    • We have long believed that phototherapy is harmless
      – However, data from the Collaborative trial of phototherapy in the US during the 1970s showed an excess mortality in infants randomized to receive phototherapy
        » Brown et al and Lipsitz et al, Pediatrics 1985
      – These findings were discounted because the differences were not significant
        » The relative risk has later been calculated to 1.36 (CI 0.96 to 1.82)
        » Wennberg R, Cell Mol Neurobiol 2000

Neonatal jaundice

Our therapies

• Phototherapy
  – Can phototherapy be harmful?
    • A reanalysis* of the Neonatal Research Network trial of aggressive phototherapy** also gives cause for concern:
      – Among mechanically ventilated infants <750 g BW, a reduction in impairment and profound impairment in the group who received "aggressive phototherapy" (AgPT) was offset by higher mortality (P for interaction <0.05) with no significant effect on composite outcomes.
      – Conservative Bayesian analyses of this subgroup identified a 99% (posterior) probability that AgPT increased mortality, a 97% probability that AgPT reduced impairment, and a 99% probability that AgPT reduced profound impairment.

Neonatal jaundice
Our therapies

- Phototherapy – where does it work?
  - Phototherapy was discovered because photo-irradiated skin became paler / less jaundiced
    - So naturally one thought that the effect of light was in the epidermis
    - Which made it reasonable to recommend turning babies in phototherapy over on the other side after a while
      - To make the more jaundiced skin on the other side accessible to the phototherapy lights
  - Recent data make it more doubtful that the principal effect of phototherapy occurs in the outer layers of the skin

From Donneborg ML et al, Acta Paediatrica 2010

Neonatal jaundice
Our therapies

| Rate of formation of photoisomers |

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Mreihil K et al, Pediatr Res 2010
Neonatal jaundice
Our therapies

• Phototherapy – where does it work?
  – The data from Donneborg et al and Mreihil et al do not seem compatible with a principal action of phototherapy in neonatal jaundice being localized to the superficial layers of the skin
  – But rather they seem compatible with a principal action occurring in the capillary circulation
  – This has therapeutic implications

• Phototherapy – how fast can it work?
  – Some years ago, in 4 extremely jaundiced infants, I showed that TSB was reduced by 10 mg/dL (170 μmol/L) in the course of 2 hours

Neonatal jaundice
Our therapies

• "Crash-cart approach"
  – The "new epidemic" of kernicterus has involved
    • Infants who were discharged home and came back with extreme jaundice
    • Delays in seeking care
    • Delays in implementing care
      – "Jaundice is normal, nothing to worry about, we'll check it tomorrow"
      – Long waiting periods in crowded emergency rooms
      – Admissions to "pediatric floors" rather than NICUs
      – Waiting for confirmatory lab reports
      – Waiting for blood for exchange transfusion
      – Less than maximally effective phototherapy
      – I.v. rather than p.o. hydration
Neonatal jaundice
Reversal of (at least) intermediate stage acute bilirubin encephalopathy may be possible

- Requires emergency action = "crash cart approach"
  - Readmitted at 4 days of age because of a 10% weight loss, irritability, and severe jaundice.
  - Triple phototherapy was started immediately and continued up to as well as between the exchange transfusions.
  - The course of bilirubin values is shown in the figure.
  - Seizures responded clinically to phenobarbital and diazepam, but continued to be present on EEG.

Neonatal jaundice
Reversal of (at least) intermediate stage acute bilirubin encephalopathy may be possible

- Requires emergency action = "crash cart approach"
  - The baby developed apneas and was ventilated mechanically for two days.
  - A brain MRI done six days after admission showed increased signal intensity in the globus pallidus bilaterally.
  - Normal neurological development on follow-up!

Neonatal jaundice
Elements of a crash-cart approach

- Systems revision
  - Identify factors in your organization of care which would cause delays in
    - Identifying an infant with treated neurotoxicity
    - Instituting treatment immediately such an infants is identified
  - Bypass ER?

- Re-education of staff
  - Neonatal jaundice may be a normal phenomenon, but that is true only after the baby has been evaluated
  - No phone advice for jaundiced babies at home –
    - They must come in and be evaluated!
Neonatal jaundice
Elements of a crash-cart approach

- In a significantly jaundiced baby
  - Do not wait for test results –
  - Start intensive phototherapy immediately
  - "Phototherapy never killed anyone"
  - Get the necessary labs for ordering exchange blood with your first set of labs
    - If the baby has neurological symptoms – order blood for an exchange transfusion STAT –
    - But do not interrupt or wait with phototherapy just because you think you’re likely to exchange the baby
    - In that scenario I would likely give the baby 1G IVIG i.v.
    - particularly if I knew the mother was type 0 or Rh-

- Check for weight loss and signs of dehydration
- Rehydrate the baby by mouth with a breast milk substitute or liberal breast milk (if the mother has enough) in order to reduce the enterohepatic circulation of bilirubin
  - unless the baby is critically ill and oral nutrition is contraindicated
  - i.v. hydration is not likely to reduce the risk of kernicterus
  - Whereas interruption of enterohepatic circulation may reduce that risk
- Even if signs of intermediate to advanced bilirubin encephalopathy are present
  - Reversal and a normal outcome may be possible
- Kernicterus continues to happen
  - But it can be prevented
  - Careful evaluation of each individual mother-child dyad before discharge
  - Education of parents (and nursing staff)
  - Clear plans for follow-up
    - Which weigh ease of access vs individual risk factors
    - Readiness for “disaster management”
  - Kernicterus could become a "never-disease"
Thank you for listening!
Muito obrigado por sua atenção (e paciência)!