Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 12 (3—4), pp. 317—321 (1971)

Neonatal Pathologic Jaundice:

Seven to Nine Years Follow-up

By

J. Rosta, Zita Makói, D. Békefi, P. Popper, Susan Szinetár, Livia Szegő, Margit Szabó, Mária Szendrői and O. Ribári

First Department of Paediatrics, First Department of Neurology and Department of Oto-Rhino-Laryngology, Semmelweis University Medical School, Budapest

(Received July 1, 1971)

Eighty-four children, 82.3% of a three-year total patient material, including all full-term babies with a history of immune-haemolytic disease or hyperbilirubinaemia, have been re-examined 7 to 10 years later. Routine examination was followed by developmental tests, neurology, electroencephalography, audiometry and psychology. All data regarding pre- and postnatal diseases, home and school behaviour were collected and analysed statistically. Physicians and other specialists worked blindly.

Severity of neonatal jaundice was graded according to the peak serum bilirubin level and its time of occurrence, CNS abnormalities were found in an overall 34, 37, and 55% of the cases in three groups with a growing severity of jaundice.

No runting was found. There was no evidence of significant extrapyramidal dysfunction. Nine cases displayed a minor cerebral dysfunction syndrome, convulsions were reported in 10 children, severe sensorineural hearing loss in 5, mild to moderate in 9 patients. Hearing loss was related to jaundice and to streptomycin treatment. Distribution of I. Q. was the same as in the normal population. Bad social and family adaptation occurred in 68% of the cases.

To clarify the intriguing question of the sequelae of pathologic neonatal jaundice is a difficult task. It is well-known that indirectly reacting bilirubin may cause a wide scope of CNS lesions ranging from grave extrapyramidal defects and hearing loss to a delicate disturbance of the cerebral cortex resulting in alterations of the highest psycho-neural functions. Hence a thorough judgement of the sequelae is impossible before school-age, when mental and psychical development are more open to scrutiny.

The difficulties met with during the organization of an extensive follow-up should not be underestimated. Finding the necessary high percentage of ex-patients 7—9 years after their neonatal hospitalization is in itself a problem. Further problems are arising when the patients are to be signed into comparable groups with similar characteristics for the affection and its treatment. It must be borne in mind that the actual state of the patients has been influenced in addition to the jaundice by a number of further factors (preconceptional, intrauterine, perinatal). Still, we have attempted to carry out a carefully controlled re-investigation of a large patient material at school age.

Material and Methods

A long-range follop-up project has been started involving children born with a weight of 2500 g or more and displaying a serum bilirubin level surpassing 15 mg/100 ml, with or without an immune-haemolytic background. Between January, 1960, and August, 1962, one-hundred and two such babies were observed in our Department. The present study includes 84 (*i.e.* 82.3%) of these newborns, with a nearly equal distribution concerning Rh and ABO immune-haemolysis, and hyperbilirubinaemia of unknown origin.

Mean age of the children was 8 years and 3 months (range 7 to 9½ years). They had all completed at least the first form of primary school, and were in a period when social adaptation and CNS abnormalities, especially their hearing could be judged more reliably than at an earlier age.

Each patient was subjected, in addition to a routine examination, to developmental tests, audiometry, psychological and neurological examination and electroencephalography.

Audiometry was performed with a Kamplex OB-3 type apparatus. In cases of suspected sensorineural hearing loss, determination of supraliminal adaptation, Ribári's exhaustion test [14] and speech-audiometry were also carried out.

The parents and schoolmasters filled in circulars supplying information about psycho-somatic progress and home and school behaviour.

The EEG was recorded by means of a 15-channel Galileo apparatus. The children were examined awake for spontaneous cerebral activity and activity after hyperventilation. Normal controls were taken from the atlas of Gibbs and Gibbs [5] and our own patient material.

All these data together with those found in the hospital records and other medical documents were coded according to specific criteria and analysed. The paediatricians and other specialists worked blindly, uninfluenced by the history, and based their judgement exclusively on actual findings.

Results

General findings

Weight, length and head circumference as compared to Hungarian percentile-charts showed apart from a slight clustering of values below the 10th and above the 90th percentiles a normal distribution. Values under the 10th percentile were not correlated with the severity of jaundice. There was no sign of hypothalamic involvement or portal hypertension. The yellow discoloration of the dental enamel, reported as a tipical finding in bilirubin encephalopathy, was not present in any of the cases.

Neurology

There was no evidence of a significant extrapyramidal dysfunction claimed to represent a typical sign of kernicterus. In eight cases, nevertheless, slight extrapyramidal dyskinesis, ataxia, impaired drawing skill etc., pointed to a subcortical lesion. In the cortical functions of the same patients, minor disabilities were evident; they corresponded to the minor cerebral dysfunction (MCD) syndrome.

Another type of multiple disturbance was present in four children with an I. Q. below 0.70, where oligophrenia was associated with severe sensori-neural hearing loss, speech-defect and retardation in motor development.

Convulsions were reported in 10 children; in 5 of them they had been provoked by febrile episodes.

Electroencephalography

Normal tracings and irregular patterns falling within the limits of normal variations were obtained in 43 cases. Twenty-two children displayed a preponderance of slow waves, further 2 a beta-wave dominance.

Definitely abnormal, paroxysmal tracings were revealed in six cases. The above findings were not correlated to neonatal jaundice; the paroxysmal electrical activity was even in negative correlation with the neonatal condition.

Audiometry

Severe sensori-neural hearing loss was detected in 5, a mild to moderate one in 9 patients. The defect was bilateral in all but two of the severely affected children. Three patients had a retrocochlear lesion. The above incidence was surpassing the frequency of similar alterations in the normal population.

Perceptive hearing loss was related to the gravity of jaundice and, in addition, to the presumable side effect of streptomycin treatment.

Psychological findings

Bad social and family adaptation was the most frequent (68%) finding at psychological sessions. An infantile-aggressive character was significantly more frequent after severe jaundice; this was not the case with introverted patients with anxieties. School performance displayed a deteriorating tendency in 30% of the patients. Fatigue, exhaustion, deconcentration were frequent even in children with fair intellectual abilities.

Distribution of I. Q. was the same as in the normal population. Four children had an I. Q. below 0.70, eleven an I. Q. in the range between 0.70—0.80. Mental ability in this last group was considered prone to improvement. The role of an unfavourable milieu was evident in the cases with a low I. Q. and in the 35% in whom a low manual intelligence was found.

Discussion

In the pertinent literature [1, 2, 4, 8, 10, 13, 16, 17] we have been unable to find a report on examinations performed at an age similar to that of our material.

In addition, we have succeeded in re-examining 82% of the original material of 102 patients, while similar studies [6, 7, 9, 10] had to content themselves with 42 to 68% of the neonatally jaundiced babies. The only study in which a higher percentage, 89%, of the original material was re-examined, is that of Culley et al. [3]; these authors have, however, only investigated cases with a bilirubin level of less than 20 mg per 100 ml and have neglected to record the EEG. In a further investigation [12] 83.4% have been re-examined; these results are invalidated by the fact that at control the age of the children ranged from six months to eight years.

It has been attempted to define the role played in the sequelae of (i) neonatal pathologic jaundice; (ii) other noxious factors; and (iii) the possible influence of exchange transfusions.

Grouping of the patients seems to be of paramount importance.

Severity of jaundice was graded according to the height and time of the peak bilirubin level, recording these data on the new indication chart for exchange transfusions developed by two of the present authors [15]. The margins of indication in the quoted study were established according to the clinical and serological states and birth-weight of the infants.

On this basis we have grouped our patients as follows.

(I) peak serum bilirubin level below the limit when an exchange transfusion comes into consideration;

(II) peak serum bilirubin level exceeding the above criteria but not representing an absolute indication for exchange transfusion;

(III) peak serum bilirubin level above the limit absolutely indicating an exchange transfusion.

Coombs positive babies, which would have belonged into groups II and III, were classified into group III in view of the special risk and their group I limit was lower than that for the others.

This grouping seemed to reflect the clinical and prognostical situation more exactly than did previous methods, when only the peak bilirubin level was considered in 5—10 mg per 100 ml brackets [4, 11, 16].

Of the present patient material 35 patients belonged to group I, 27 to group II, and 20 to group III. Two patients were not classified: one died with pneumonia at the age of three months, and the other contracted a tuberculous meningitis at the age of four years.

Summing up all the findings in the three groups, sequelae were found in 34, 37 and 55%, respectively. As an overall 50% of the babies with a history of some disease in addition to the jaundice were also included into the study, at the control examinations a high incidence of deviations (especially cortical lesions) was found even in the babies whose neonatal jaundice had been slight. The more than 20% difference in abnormalities in group III *vs* groups I and II may thus be attributed to the effect of severe neonatal hyperbilirubinaemia.

In search of the influence of exchange transfusions we have taken into consideration only cases with a positive anti-human globulin test and those classified into group II since these belonged to the category where, according to the earlier conservative policy there was an absolute indication for blood exchange. Twenty-one of these children had been subjected to an exchange-transfusion, whereas 10 had had been treated without it; still, there was no difference whatever in the ratio of sequelae. This proves that the criteria for exchange transfusion therapy outlined in our new diagram are justified.

References

1. Ballowitz, L., Stück, B.: Spätschäden nach schweren Neugeborenenicterus. Pädiat. prax. **3,** 9 (1964).
2. Bjure, J., Liden, G., Reinand, T., Vestby, A.: A follow-up of hyperbilirubinaemia in full-term infants without isoimmunization. Acta paediat. scand. **50,** 437 (1961).
3. Culley, P., Powell, J., Waterhouse, J., Wood, B.: Sequelae of neonatal jaundice. Brit. med. J. **3,** 363 (1970).
4. Boggs, T. R. Jr., Hardy, J. B., Frazier, T. M.: Correlation of neonatal serum total bilirubin concentrations and developmental status at age eight months: A preliminary report from the collaborative project J. Pediat. **71,** 553 (1967).
5. Gibbs, F., Gibbs, E.: Atlas of electroencephalography. Addison Wesley Press Cambridge, Mass. 1950—52.
6. Holmes, G. E., Miller, J. B., Smith, E. E.: Neonatal bilirubinemia in production of long-term neurological deficits. Amer. J. Dis. Child. **116,** 37 (1968).
7. Hyman, C. B., Keaster, J., Hanson, V., Harris, I., Sedgwick, R., Wursten, H., Wright, A. R.: CNS abnormalities after neonatal hemolytic disease or hyperbilirubinemia. Amer. J. Dis. Child. **117,** 395 (1969).
8. Johnston, W. H., Angara, V., Baumal, R., Hawke, A. W., Johnson, R. H., Kett, S., Wood, M.: Erythroblastosis fetalis and hyperbilirubinemia. (A five-year follow-up with neurological, psychological and audiological evaluation.) Pediatrics **39,** 88 (1967).
9. Keaster, J., Hyman, C. B., Harris, I.: Hearing problems subsequent to neonatal hemolytic disease or hyperbilirubinemia. Amer. J. Dis. Child. **117,** 406 (1969).
10. Killander, A., Michaelsson, M., Müller-Eberhard, V., Sjölin, S.: Hyperbilirubinemia in full-term infants without isoimmunization: A follow-up study. Acta paediat. scand. **52,** 481 (1963).
11. Koch, C. A.: Hyperbilirubinemia in premature infants. A follow-up study II. K. Pediat. **65,** 1 (1964).
12. Ose, T., Tsuruhara, T., Araki, M., Hanaoka, T., Bush, O. B.: Follow-up study of exchange transfusion for hyperbilirubinemia in infants in Japan. Pediatrics, **40,** 196 (1967).
13. Preisler, O., Gronau, M., Horstman, W.: Morbus haemolyticus neonatorum und spätere Entwicklung der Kinder. Dtsch. med. Wschr. **88,** 1823 (1963).
14. Ribári, O.: The effect of noise of different types to the hearing adaptation and fatigue. IVth Conference on Acoustics. Vol. II. 19 A 3. Budapest 1967.
15. Rosta, J., Békefi, D.: A new chart for indicating exchange transfusion in neonatal hyperbilirubinaemia. Acad. paediat. Acad. Sci. hung. **12,** 311 (1971)
16. Wishingrade L., Cornblath, M., Takakuwa, T., Rozenfeld, I. M., Elegant, L. D., Kaufman, A., Lassers, E., Klein, R. I.: Studies of non-hemolytic hyperbilirubinemia in premature infants. I. Prospective randomized selection for exchange transfusion with observations on the levels of serum bilirubin with and without exchange transfusion and neurologic evaluation one year after birth. Pediatrics, **36,** 162 (1965).
17. Wohlmuth, G., Fráter, R.: Katanamnestische neurologische Untersuchungen bei Icterus gravis. Acta paediat. Acad. Sci. hung. **2,** 173 (1961).

Dr. J. Rosta
Bókay J. u. 53
Budapest VIII., Hungary