EXTENDED REPORT

Normal neuropsychological development in children with congenital complete heart block who may or may not be exposed to high-dose dexamethasone in utero

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Background: Antenatal and postnatal treatment with dexamethasone (DEX) may negatively affect the neuropsychological development in children. Maternal anti-Ro/Sjögren's syndrome A (SSA) antibodies may also be associated with learning disabilities in offspring.
Objective: To assess neuropsychological development in babies exposed to very high dosages of DEX in utero, whose mothers were anti-Ro/SSA positive.
Methods: 13 children with congenital complete heart block (CHB) (11 exposed and 2 not exposed to DEX) and 3 healthy siblings, all of anti-Ro/SSA-positive women, were evaluated. 11 preschool-aged children (5 boys) were assessed using Griffiths Mental Development Scales. 5 school-aged children (2 boys) were examined using Wechsler Intelligence Scale for Children—Revised to check IQ and reading tests to explore the existence of learning disabilities or dyslexia. None of the children had had major neonatal complications, although those with CHB had to be paced at different intervals from birth.
Results: The children had been exposed in utero to a mean total dose of 186.6 mg DEX. IQ levels were always normal (mean IQ 105.1, standard deviation (SD) 9.5). Only one child had a learning disability, of borderline clinical significance, but this child had never been exposed to DEX.
Conclusion: No negative effects were found on the neuropsychological development in this cohort of children, even if they had been exposed to maternal anti-Ro/SSA antibodies and to very high dosages of DEX (much higher than those used to improve fetal lung maturity). These findings might be of interest in view of the large number of infants exposed in the past to repeated antenatal courses of steroids.

Findings in animals[1–3] and humans[4–7] suggest that antenatal and postnatal treatment with dexamethasone (DEX) may negatively affect neuropsychological development in infants. In addition, the presence of maternal anti-Ro/Sjögren's syndrome A (SSA) antibodies may be associated with learning disabilities in offspring.[8]

Small trials support the benefit of fluorinated steroids in the treatment of congenital heart block (CHB),[9 10] which occurs in utero in approximately 1–2% of anti-Ro/SSA-positive mothers,[11 12] but the question remains controversial. Usually, DEX 4 mg daily is given to prevent progression of incomplete heart block to the fibrotic irreversible state of complete CHB, or to treat myocarditis or fetal hydrops.[13] These fetuses are exposed to much higher dosages of DEX or bethametasone than the single course of 24 mg usually given to pregnant women at risk of preterm delivery to reduce the risk of death, respiratory distress syndrome and cerebral haemorrhage in their premature infants.[14]

Our study assessed neuropsychological development in a small cohort of babies exposed to very high dosages of DEX in utero, whose mothers were also anti-Ro/SSA positive. CHB is a rare condition, but our findings may be clinically relevant in view of the large number of newborns who were exposed in the past to repeated courses of antenatal steroids to induce fetal lung maturity.

PATIENTS AND METHODS

Patients

From 1992 to 2004, we observed 17 babies born with complete CHB, most of whom had been treated in utero with high-dose DEX. Three died soon after birth from intractable heart failure; another, born in August 2001, developed severe dilated cardiomyopathy in 2002, and his parents did not consent to his enrolment in this study. We investigated the remaining 13 babies. There was one twin pregnancy and one of triplets; only one of the twins and one of the triplets had complete CHB, but we studied the other three as well, as they had been exposed to the same dose of DEX in utero. Thus a total of 16 children were studied. Table 1 summarises their clinical features. All were delivered by caesarean section.

Mean weight (standard deviation (SD)) was 2033 (505) g and mean (SD) gestational age was 35.1 (2) weeks at birth. In all, 11 infants (68.7%) were born preterm (<37 weeks of gestational age) and 6 (37.5%) were small for gestational age (<10th centile for birth weight). Three infants small for gestational age also had a small cranial circumference for their gestational age; the others were all normal. They all were in good clinical condition, as is usual in surviving babies with complete CHB,[15] with an uneventful clinical course. No complications were seen in terms of the common diseases or pathologies, sometimes very severe, which may affect the preterm newborn and consequently, later in life, exert a negative influence on neuropsychological development. All were paced, at different ages (table 1). None developed clinical features of autoimmune conditions or of

Abbreviations: CHB, complete heart block; DEX, dexamethasone; SSA, Sjögren's syndrome A; WISC—R, Wechsler Intelligence Scale for Children—Revised

Table 1 Newborn features, date of birth and age of permanent pacing

Patient	Sex	Year of birth	GA CHB	Lower fetal HR	GA at delivery	HR at birth	Apgar score	Fetal heart failure	DEX exposure (mg)	Birth weight (g)	Centile	Birth HC (cm)	Centile	Age of permanent pacing
1	M	2002	24	55	35	40	5–8	No	242	2080	25	32	50	7 days
2	M	2002	24	45	34	45	5–8	Pericardial effusion	196	1640	3–10	NR	NR	5 weeks
3	F	2002	NA	NA	34	110	9–9	No	196	1630	3–10	NR	NR	
4	F	2001	24	52	33	50	5–8	Hydrous	160	1870	25	NR	NR	6 weeks
5	F	2001	NA	NA	33	110	8–9	No	160	1900	25–50	NR	NR	
6	M	2001	NA	NA	33	115	9–9	No	160	1870	50	NR	NR	
7	F	2001	18	70	35	80	9–9	No	551	2050	10–25	35	97	11 months
8	M	2000	20	50	38	60	8–9	No	0	2900	25	32	3	2 days
9	F	2000	20	62	38	70	8–9	No	240	2900	50	32	10	3 months
10	M	2000	20	55	32	50	9–9	No	84	1300	3–10	25	<3	2 months
11	F	1998	20	47	33	48	9–9	No	260	1430	3–10	25	<3	30 days
12	M	1997	23	62	33	50	8–9	No	95	1645	10–25	30	25	3 months
13	F	1996	32	30	36	58	8–9	No	84	2770	50–75	33.5	75	3 days
14	F	1995	26	60	38	52	8–9	No	240	2600	10–25	32	10	8 months
15	F	1992	29	50	37	50	9–9	No	0	2050	3	32.5	25	10 years
16	M	1996	21	64	38	60	8–9	No	318	1900	<3	33	10–25	3 years
Mean			23.2	54	35.1	54.8			186.6	2033.4				
Range			18–32	30–70	32–38	40–80			0–551	1300–2900				

CHB, complete heart block; DEX, dexamethasone; F, female; GA CHB, gestational age at detection of CHB; HC, head circumference; HR, heart rate; M, male; NA, not applicable; NR, not registered.
Patients 3, 5 and 6 did not have CHB.

immunodeficiency. The babies were exposed in utero to a mean total dose of 186.6 mg DEX (range 0–551; table 1): 14 babies had been treated in utero with high-dose DEX, whereas two (patients 8 and 15) were exposed only to a single course of bethamethasone (24 mg) but not to DEX, as they came to our attention only for delivery. However, we included them as internal controls—that is, babies with CHB exposed to anti-Ro/SSA antibodies but not to DEX. All of the 13 mothers were anti-Ro/SSA positive; 7 had an undifferentiated connective tissue disease and 6 had primary Sjögren's syndrome. Antibodies to Ro/SSA were determined by counterimmunoelectrophoresis and immunoblotting as previously described.[16]

Methods

At the time of this study, the children's mean age was 5 (range 2–12) years. The Niguarda Hospital internal review board approved the protocol. With the parents' written informed consent, 16 children were included in this study in 2004. Eleven were of preschool age (mean age 30.1, range 14–65 months) and five of school age (7–11 years).

To evaluate the development of children aged <6 years, we used the Griffiths Mental Development Scales,[17] which evaluate mental age in relation with chronological age and a general developmental quotient (IQ), which is the average of six different items (locomotor, personal–social, hearing and speech, hand and eye coordination, performance and practical reasoning scales). For children aged >6 years, we used the Wechsler Intelligence Scale for Children—Revised (WISC-R),[18] which comprises verbal and performance tests, for assessing a total IQ, a verbal IQ and a performance IQ. To directly evaluate any learning disabilities, children aged >7 years were also tested for reading skills, using test numbers 4 and 5 of the Sartori test[19] and the MT test[20]; these measure the speed and correctness of reading. In addition, a thorough neuropsychiatric assessment of the children and their behaviour was carried out during the tests. A diagnosis of learning disability can be made when the results are lower than 2 SD from the mean for the general population of the same age and IQ.

RESULTS

Tables 2 and 3 summarise the results of preschool-aged and school-aged children, respectively. The mean IQ was 105.1 (range 91–121, median 104, SD 9.5). Mental retardation is defined by an IQ of <70, so all 16 children were of normal intelligence. We found no significant differences between mental age and chronological age for the 11 preschool infants and the developmental quotient was always within the normal range ($p>0.01$).

All five school children had a total IQ in the normal range. The child with congenital sensorineural deafness (patient

Table 2 Results of Griffiths test in preschool children

Patient	Sex	DEX exposure (mg)	Chronological age (months)	Mental age (months)	Developmental quotient (nv>70)
1	M	242	14	13	95
2	M	196	20	20	112
3	F	196	20	20	114
4	F	160	29	29	101
5	F	160	29	31	106
6	M	160	29	31	107
7	F	551	34	31	91
8	M	0	42	50	121
9	F	240	45	53	118
10	M	84	48	48	101
11	F	260	65	60	93

DEX, dexamethasone, F, female; M, male.
Patients 3, 5 and 6 did not have complete heart block.

13), whose father and one sibling had the same congenital defect, showed a marked discrepancy between verbal IQ and performance IQ, clearly related to the deafness; however, the IQ was still normal, thanks to an excellent performance IQ. Owing to deafness, decoding ability and text understanding were not tested in this child.

In child 15, a discrepancy was observed between decoding ability and reading tests, and this will need to be checked during follow-up. This baby was not exposed to DEX in utero.

As regards maternal side effects related to DEX, the mother of patient 9 developed transient incapacitating insomnia and the mother of patient 10 had a recurrence of a transient acute psychosis; both were concurrently treated with high-dose salbutamol. As regards the fetuses, it is difficult to relate the mild prematurity and some cases of oligohydramnios to DEX or to the global course of the pregnancy complicated by CHB.

DISCUSSION

Liggins[21] in 1972 first showed that treating women with betamethasone almost halved the incidence of respiratory failure in the offspring. Despite increasing evidence of the benefit of antenatal corticosteroids over the ensuing two decades, obstetricians were slow to adopt them. To assess the effectiveness of this antenatal treatment, the National Institutes of Health sponsored a Consensus Development Conference in 1994 on how corticosteroids for fetal maturation affected perinatal outcomes. The consensus panel concluded that a single course of corticosteroids (betamethasone or DEX, 24 mg) given to pregnant women at risk of preterm delivery, between 24 and 34 weeks of gestational age, clearly reduced the risk of death, respiratory distress syndrome and cerebral haemorrhage in their preterm infants.[14] Since then, this practice has became more popular among doctors, and it is now common practice among obstetricians to prescribe weekly antenatal steroid courses to women undelivered after the first dose.[22]

However, accumulated evidence suggests the potential harm of repeated courses of steroids for the mother and the fetus. Findings on animals widely suggest that repeated antenatal doses of steroids can interfere with the growth and development of the immature brain[1–3] and observations on humans suggest that antenatal and postnatal DEX may negatively affect the child's neuropsychological development.[4–6] Furthermore, postnatal magnetic resonance indices of infant brain maturation suggest a potential negative effect of multiple antenatal steroid doses.[23] Recent data suggest that rates of disabilities and educational difficulties are high in infants with neonatal chronic lung disease, but with no marked differences between infants treated and those not treated with DEX.[24] Prematurity itself is associated with mild brain structural differences that persist at 8 years of age, with associated lower neurocognitive scores, but perinatal hydrocortisone had no long-term effects on either neurostructural brain development or neurocognitive outcomes.[25]

These data on animals and humans refer almost exclusively to fluorinated steroids, and doses applied were lower than those used in our cohort of children.

The possible negative effects seem to be linked more to DEX than to betamethasone,[6] and it has been suggested that betamethasone should be preferred when available.[7 26] A separate meta-analysis of the data in the Cochrane Review shows that only betamethasone and not DEX considerably reduces neonatal mortality.[27] In view of this concern, another National Institutes of Health Consensus Conference in 2000 confirmed the previous statement of the advantages of one course of antenatal corticosteroids but also made it clear that, considering their potential hazard, repeated courses should not be given routinely but reserved for patients in randomised controlled clinical trials.[28]

Small trials support the benefit of fluorinated steroids in the treatment of children with CHB of anti-Ro/SSA-positive mothers,[9 10] although the question remains controversial. The presence of maternal anti-Ro/SSA antibodies as such may be associated with learning disabilities in offspring.[8] In the light of these findings, babies with CHB who are both treated in utero with high-dose DEX and exposed to maternal anti-Ro/SSA antibodies should be at very high risk of neurodevelopmental defects.

Recently, 28 questionnaires were evaluated from families enrolled in the Research Registry for Neonatal Lupus on neuropsychiatric development in 15 affected children (10 with CHB and 5 with neonatal lupus rash) and 13 unaffected siblings, all exposed to maternal anti-Ro/SSA antibodies.[29] Of the 10 children with CHB, five were reported by a doctor, nurse or teacher to have a neuropsychiatric disorder (three had attention disorders, two had behavioural problems requiring drugs, one had behavioural and speech problems and one had depression); also for three children with CHB, parents reported that they had difficulty concentrating and paying attention. Of the five children with neonatal lupus rash, one had depression, one had vision and speech problems and one parent-reported difficulty concentrating and paying attention. A similar high frequency of neuropsychiatric disorders was observed in the 13 unaffected anti-Ro/SSA-exposed children: one had anxiety and speech problems, two had speech problems, one child was receiving drugs for an attention problem, and two had parent-reported difficulty concentrating and paying attention. The possibility of sampling bias clearly exists, as the authors acknowledge, and these children were not formally tested using neuropsychiatric scales.[29]

In view of this background, we were worried about our patients with CHB and decided to test them formally for neuropsychological development, IQ and learning disabilities. All of them had normal IQ; only one school girl had a mild learning disability, expressed by a discrepancy between decoding ability and reading test, but she was one of the two babies who was never exposed to DEX in utero. Cranial circumference values at birth were normal for gestational

Table 3 Results of Wechsler Intelligence Scale for Children—Revised test in school children

Patient	Sex	Age in 2004	DEX exposure (mg)	IQ (nv>70)	Verbal IQ (nv>70)	Performance IQ (nv>70)	Decoding ability (quick reading)	Text understanding
12	M	7 y	95	96	88	105	Age adequate	Age adequate
13	F	7 y 11 m	84	100	72	133	Not assessed	Not assessed
14	F	8 y 3 m	240	118	118	112	Age adequate	Age adequate
15	F	11 y 5 m	0	100	100	101	Age adequate	−0.94SD
16	M	7 y 6 m	318	109	120	95	Age adequate	Age adequate

DEX, dexamethasone; F, female; m, months; M, male; nv, normal value; WCIS—R, Wechsler Intelligence Scale for Children—Revised; y, years.
Patient 13 has congenital sensorineural deafness.

Figure 1 An 8-year-old girl, shown dancing, was permanently paced at the age of 8 months and was exposed in utero to a total dose of 240 mg dexamethasone; her IQ is 118 (published with her parents' written consent).

age, except in three children who had a small cranial circumference for their gestational age.

We studied only a small cohort of patients, with a relatively short follow-up, but they were exposed to very high antenatal dosages of DEX. The small number means we cannot draw any firm conclusion about any hypothetical negative effects on brain development or function. In addition, in children aged <5 years, there is considerable individual variability, making it difficult to assess subtle neurocognitive deficits. As regards possible attention-deficit hyperactivity disorder and other behavioural problems that would not be scored on the IQ testing, the normal responses to test numbers 4 and 5 of the Sartori test[19] and of the MT test,[20] and particularly the observation of the child's behaviour during the tests, enabled our neuropsychiatrists to exclude this risk.

Interestingly, in our small sample of children with CHB, we did not find the bias possibly present in other studies, as there were no cases of the severe pathologies that often affect preterm newborns and can influence brain damage, and hence neurological impairment.[24] We did not have the selection bias that might have been present in the other similar report.[29]

On the basis of the data from the literature,[6 7 26 27] we are now using bethametasone in patients with incomplete CHB or hydropic CHB, like others.[30] We were reassured to see that all our patients with CHB had normal IQ, with no learning disabilities, despite the exposure to high-dose DEX and to maternal anti-Ro/SSA antibodies. Although, it is quite possible that a repeated course of DEX may be detrimental to the newborn's neurodevelopment, a child's final intellectual maturation remains an extremely complex process, involving the interplay of many biological, social and cultural factors (fig 1).

In conclusion, we observed no negative effects on the neurodevelopment in our cohort of children, many of whom were exposed to very high dosages of DEX (much higher than those used to improve fetal lung maturity) and to maternal anti-Ro/SSA antibodies. CHB is a rare condition, but these reassuring findings might be clinically relevant in view of the large number of newborns treated in the past with repeated courses of antenatal fluorinated steroids to induce fetal lung maturity.

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