Paper IV

Pregnancies and deliveries in patients with Charcot–Marie–Tooth disease

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Abstract—*Objective:* To investigate the effect of maternal Charcot–Marie–Tooth disease (CMT) on pregnancy and delivery. *Methods:* Data from the Medical Birth Registry of Norway 1967 to 2002 were surveyed. This registry has compulsory notification of all births. One hundred eight births by mothers with CMT were identified. The reference group consisted of all 2.1 million births by mothers without CMT. *Results:* Women with CMT had a higher occurrence of presentation anomalies (9.3 vs 4.5%; $p = 0.04$) and bleeding post partum (12.0 vs 5.8%; $p = 0.02$). The rate of operative delivery was twice that of the reference group (29.6 vs 15.3%; $p = 0.002$), and forceps was used three times as often in the CMT group (9.3 vs 2.7; $p < 0.001$). The majority of CMT cesarean sections were emergency sections. *Conclusion:* Charcot–Marie–Tooth disease increases the risk for complications during delivery, which is linked to a higher occurrence of emergency interventions during birth.

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There have been few studies on how Charcot–Marie–Tooth disease (CMT) can affect pregnancy, birth and the newborn.[1-3] There has been more emphasis on diagnosis in the fetus.[4,5] We sought to examine how CMT affects pregnancy and the birth process. With use of data from the Medical Birth Registry of Norway (MBRN), a complete national survey of births in Norway from 1967, we found that CMT is an independent risk factor for complications during pregnancy and delivery.

Methods. MBRN was established in 1967 and is based on the compulsory notification of all births in Norway after 16 weeks of gestation.[6] The notification form is sent within 9 days after birth or discharge from the maternity clinic. The registry contains data on the mother's demographic variables, the pregnancy, the delivery, and the newborn. An unchanged birth notification form was in use from 1967 to 1998. A revised and more detailed form has been used since December 1, 1998. Complete ascertainment of the births is ensured through a record linkage with the National Population Registry run by Statistics Norway. The registry is placed under the Norwegian Institute of Public Health.

The data comprised all births registered in MBRN between January 1, 1967, and December 31, 2002. Through the unique 11-digit personal identification of all inhabitants in Norway, we traced the births of each mother consecutively. The CMT group consisted of all births by mothers who for at least one birth had been recorded with a CMT diagnosis: 108 births by 49 mothers. The reference group consisted of all births by women without a CMT diagnosis at any birth (n = 2,102,971).

The CMT diagnosis was established through clinical and neurophysiologic examinations as well as inheritance patterns, according to international standards,[7,8] described by a Norwegian expert group in 2001.[9] In two Norwegian studies, both published in 2001,[10,11] all patients were diagnosed with CMT on the basis of both clinical and neurophysiologic (neurography, electromyography) examinations. Genetic testing[12] was done routinely from 2001 in cases where the diagnosis was suspected (Department of Medical Genetics, Haukeland University Hospital, Bergen, Norway).

The information in the birth notification form is based on three elements: 1) a standardized form used during pregnancy by the patient's physician, 2) oral information given by the patient when admitted to the hospital, and 3) information from doctor and midwife about the actual delivery and the newborn. Thus, the notification form contains information on the mother's health before and during pregnancy as well as information about the actual birth and the newborn. Completion of the notification form is the responsibility of the attending midwife. The form is co-signed by the attending physician.

Variables. Descriptive variables included year of birth, type of obstetric institution, age of mother (completed years), sex of child, birth order (parity), birth weight (g), and gestational age in completed weeks/prematurity. Preterm birth was defined according to the World Health Organization as delivery prior to 37 completed weeks of gestation. Selected outcome variables included induction of birth (any induction, perforation of amniotic membranes, infusion with oxytocin and prostaglandin), interventions (any intervention, perforation of amniotic membranes, cesarean section, use of vacuum extractor or forceps, and manual removal of placenta), delivery complications (any complication, premature rupture of amniotic membranes, functional disorder of birth, injuries in the birth canal, bleeding post partum of >500 mL, obstruction of birth process, presentation anomalies, and complications regarding the umbilical cord), perinatal mortality, congenital conditions, and birth defects. After 1988, cesarean sections were classified as elective or not. Functional disorder of birth is a collective term for prolonged delivery (lasting >24 hours), cervical dystocia, uterine atony, and uterine dysfunction. Perinatal mortality was defined as all fetal deaths after 16 weeks of gestation as well as deaths during the first week of life. The birth defects were defined as severe and not severe, according to a definition by MBRN based on the International Classification of Diseases, 8th rev. (1967 to 1998) and 10th rev. (1999 to 2002).

Statistics. We compared the CMT and reference group using cross-tables with Pearson χ^2 test. Two-sided p values of <0.05 were interpreted as significant. Arithmetic mean was calculated for each group regarding gestational age, gestational weight, mother's age, and parity. The analyses were based on crude and adjusted measures. The following were considered as potential confounders: mother's age in completed years at birth (<25, 25 to 34, 35+), period of birth (1967 to 1980, 1981 to 1990, 1991 to 2002), birth order (first child, second child, third or more child), and type of birth institution (university hospital, other). Logistic

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Table 1 Demographic characteristics in CMT and reference group

Characteristic	CMT group	Reference group	*p* Value*
Total no. of deliveries	108	2,102,971	—
1967–1980	14 (13.0%)	40.1%	
1981–1990	47 (43.5%)	25.8%	
1991–2002	47 (43.5%)	34.1%	
Mean maternal age, y	28	27	0.9
Sex of children			
Boys	58 (53.7%)	51.4	1.0
Girls	50 (46.3%)	48.5	
Mean birth order	1.8	2.0	0.1
Mean gestational age, wk	39.6	39.6	1.0
Mean birth weight, g	3,409	3,487	0.2
Place of birth, %			
University hospital	32.4	25.4	
Nonuniversity institution	67.6	74.6	0.2

* Pearson χ^2, *p* value.

CMT = Charcot–Marie–Tooth.

regression was performed. To avoid assumptions of linear associations, all covariates were represented as indicator variables in the model. The presented adjusted results are based on adjustment for period of birth, as this was the only variable that changed the estimates. The analyses were performed in SPSS 11.0 (SPSS, Chicago, IL). Estimates of necessary sample size to obtain an 80% power to detect significant differences in use of intervention between the reference group and the patient group were calculated in S-Plus (version 6.1 for Windows). The power calculations were based on the observed proportions of intervention in the two groups, a type 1 error of 5.0%, and a two-sided test.

Results. We identified 108 births by 49 women with a diagnosis of CMT in one or more of their births (table 1). The diagnosis was positively recorded in 66 of the 108 births. Twenty-four of the 49 women had the CMT diagnosis recorded in all their births. Thirty-three were recorded with the CMT diagnosis in one birth, 15 in two births, and 1 woman in three births. No differences were found regarding mean birth weight, mean birth order (parity), mean gestational age, or prematurity comparing the CMT group and the reference group.

The rate for operative delivery (cesarean section and vacuum/forceps) was significantly increased in the CMT group (table 2). This was due mainly to an increased rate of forceps. In contrast, total interventions during birth did not occur more frequently in the CMT group. Cesarean section was performed in 17 CMT cases. Five were undertaken because of a fetal presentation anomaly. Among the remaining 12 cases, child asphyxia was notified in 1, preeclampsia in the mother in 1, and pelvic contractures in 3. Only 3 of the 10 cesarean sections performed after 1988 were classified as elective, 1 of them due to fetal hydrocephalus. The remaining seven were emergencies; in six of them, the mother had the CMT diagnosis notified. The number of births requiring any induction (infusion of oxytocin or pitocin, perforation of amniotic membranes) was not raised in the CMT group (12.0 vs 13.3% in the reference group; $p = 0.7$). The use of forceps was related to abnormal fetal presentation in 2 of 10 cases (both with abnormal cephalic presentation).

The total use of operative delivery was more stable in the CMT group than in the reference group over time (table 3). The main difference between the CMT group and the reference group was that the use of forceps in the CMT group continued to be higher in all periods (see table 3). There were few or no differences regarding use of vacuum and total number of cesarean section. As for these two procedures, a power analysis was carried throughout to evaluate our results. For cesarean section, where the proportion was 9.0% in the reference group and 15.7% in the patient group, 183 CMT patients and a correspondingly higher number of individuals in the reference group would have been necessary to obtain an 80% power to detect a significant difference in the cesarean section rate between

Table 2 Interventions during birth and obstetric complications in women with CMT (n = 108) and reference group (n = 2,102,971), adjusted for period of birth

	CMT group, n (%)	Reference group, %	Odds ratio	*p* Value*
Total interventions	36 (33.3)	22.5	1.4	0.09
Total operative delivery: cesarean section and vacuum/forceps	32 (29.6)	15.3	1.9	0.002
Cesarean section				
Total	17 (15.7)	9.0	1.5	0.1
Elective†	3 (2.8)	2.0	1.4	0.6
Forceps	10 (9.3)	2.7	3.4	<0.001
Vacuum	6 (5.6)	3.9	1.3	0.6
Total complications	46 (42.6)	36.3	1.1	0.7
Presentation anomalies	10 (9.3)	4.5	2.0	0.04
Bleeding post partum	13 (12.0)	5.8	2.0	0.02

* Pearson χ^2, *p* value.
† Data from 1988 onward.

CMT = Charcot–Marie–Tooth.

Table 3 *Operative delivery in CMT (n = 108) and reference (n = 2,102,971) group according to period of birth*

Procedure/period of birth	CMT group, n (%)	Reference group, %	Rate ratio	*p* Value*
Total operative deliveries				
1967–1980	3 (21.4)	8.6	2.5	0.09
1981–1990	17 (36.2)	18.6	1.9	0.002
1991–2002	12 (25.5)	20.5	1.2	0.4
Cesarean section				
1967–1980	0	3.9	—	—
1981–1990	10 (21.3)	11.3	1.9	0.03
1991–2002	7 (14.9)	13.2	1.1	0.8
Forceps				
1967–1980	3 (21.4)	2.3	9.3	0.0001
1981–1990	4 (8.5)	3.9	2.2	0.1
1991–2002	3 (6.4)	2.1	3.0	0.045
Vacuum				
1967–1980	0	2.5	—	—
1981–1990	3 (6.4)	3.8	1.7	0.4
1991–2002	3 (6.4)	5.6	1.1	0.8

* Pearson χ^2, *p* value.

CMT = Charcot–Marie–Tooth.

the two groups. Thus, the number needed was close to the actual 108 patients, and power was found not to be decreased considerably. As for vacuum extraction, where the proportion was 3.9% in the reference group and 5.6% in the patient group, the necessary number of CMT patients would have been 1,195 to detect a significant difference.

Presentation anomalies for the child occurred with increased frequency in the CMT group (see table 2). Breech presentation was recorded in four births and abnormal cephalic presentation in six.

Increased bleeding post partum occurred more commonly in the CMT group (see table 2). Among the 13 cases with bleeding, 2 women had undergone cesarean section, 4 had uterine dysfunction and uterine atony notified, and 2 had retained placental fragments. In five cases, no other complication or condition was notified.

The total rate of birth complications was not raised in the CMT group (see table 2). No increased incidence was found for obstruction of the birth process (3.7% in the CMT group vs 1.9% in the reference group; $p = 0.3$) or for functional disorder of birth or injuries in the birth canal (8.3% in the CMT group vs 6.5% in the reference group; $p = 0.7$). No increased incidence was found for premature rupture of amniotic membranes. The perinatal mortality for the CMT group was not raised compared with the reference group (1.9 vs 1.6%; $p = 0.9$). One CMT child was born with hydrocephalus and another with foot deformities. The total rate of severe birth defects was not increased compared with the reference group (1.9 vs 1.9%; $p = 1.0$).

Discussion. Women with CMT more frequently needed operative intervention during delivery. Forceps and vacuum were employed twice as often in this group. The majority of cesarean sections performed on women with CMT were undertaken as emergencies. Both presentation anomalies and bleeding post partum occurred more frequently in the CMT group, the risk doubled compared with the reference group.

There is convincing evidence that this study includes all women with CMT giving birth in Norway from 1967 to 2002. We were able to link each mother's consecutive births, and this showed a high consistency in the diagnosis of CMT for consecutive births, suggesting no or a very low proportion of false positives in our data set. This is important, as false positives would have diluted any effects.

Norway has until recently had a low total rate of cesarean section, and the rate is still substantially lower than in many other countries: 15.1% in 2002 compared with 26.0% in the USA.[13,14] As the policy toward cesarean section has become less restrictive, there has been a tendency toward performing elective sections in patients considered with an increased risk.[15] There was no such trend among the mothers with CMT. The majority were emergency sections, both when the diagnosis was recorded on the birth registration form and when it was not. This implies that the mother's clinical condition prior to delivery—and her disorder—were not regarded as representing any increased risk. The frequent use of the emergency procedures of vacuum and forceps in the CMT group supports this theory. Contrary to the general trend in obstetric care,[16] the use of forceps in the CMT group remained high throughout the whole time period, further demonstrating the real need for emergency delivery in mothers with CMT.

Presentation anomalies occurred more frequently in the CMT group than in the reference group. This is similar to what is seen for myotonic dystrophy.[17] However, in myotonic dystrophy, the fetus is fre-

quently severely affected by the mother's genetic disease with marked muscle weakness. Several risk factors have been linked to abnormal presentation at birth, but the most common ones such as low birth weight, primiparity, and preterm delivery did not occur more frequently in the CMT group. However, infants with a neonatal morbidity more frequently have an abnormal birth presentation.[18,19] A preexisting motor disorder in the fetus increases the likelihood of abnormal presentation.[20] Fetal kicking is an important determinant for presentation at birth, and the weaker the lower-extremity musculature, the more likely is a fetus to present in an abnormal position.[21] In this register-based study, it was not possible to retrieve information on whether the newborn had inherited the maternal CMT gene. But as CMT is a dominant disease, one-half of the 106 children should have inherited the disorder. Although usually recognized at a later age, muscle weakness and wasting as well as hypotonia have been described during the first year of life.[22] When symptoms occur at such an early age, one could as well assume functional motor changes already in utero. Thus, the children presenting in an abnormal position may not only reflect the maternal disease but also the fetal genotype.

Bleeding post partum was more common in the CMT group. In the general population, uterine atony is the most common cause for postpartum bleeding,[23] and it is tempting to assume that CMT as a hereditary neuropathy or the CMT gene defect can influence uterine function. A CMT effect on the diaphragm and the function of upper airways due to neuropathy of the phrenic and pharyngeal nerves has been described.[24,25] Vagus nerve dysfunction with vocal fold paresis and autonomic failure with dysfunctional anal sphincter and urinary bladder have been reported as well.[26-28] Thus, a CMT-mediated neuropathy of the uterine adrenergic nerves is probable. Neural degeneration could affect the contractility of the organ, leading to hypotony and failure in contracting after birth, explaining the increased bleeding. Uterine atony occurred with an increased frequency in our CMT mothers. Pregnancy is associated with adrenergic nerve degeneration in the uterus, caused by sex steroids.[29] This gestational nerve loss seems to be more widespread when the peripheral nervous system is already damaged.[3] The high levels of sex steroids during pregnancy, in particular progesterone, were instrumental for the progression of CMT nerve damage in a rat model.[30]

CMT is a genetically heterogeneous disorder, but axonal damage is the major cause for weakness and disability in all forms of CMT.[31] CMT has up till now been acknowledged as a disease mainly affecting distal extremities with no significant effect on pregnancy, delivery, and the newborn.[32] The results from our study question this view and show that maternal CMT should be considered as a potential risk factor during delivery.

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