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Case report

# Neonatal neuroblastoma and *in utero* exposure to progestagens

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**Abstract.** We report a case of neonatal neuroblastoma occurring in a boy who had been exposed *in utero* to progestagens. The potential role of therapeutic products administered during pregnancy in the occurrence of neuroblastoma is reviewed, with emphasis on sex hormones and in particular progestagens.

Despite the recognition of the fact that neuroblastoma is the most frequent solid tumour in the first year of life and also that treatments with progestagens in pregnancy are common in several countries, therefore potentially leading to co-incidental association, some arguments in favour of a causal link come from the few epidemiological studies validly assessing this association. Also discussed is a possible association of childhood malignancy with threatened abortion or uterine contractions, as some sort of disturbed hormonal status may be a risk factor for both threatened abortion and child cancer.

## 1. Introduction

Neuroblastoma is the most common solid tumour of infancy, accounting for 50% of all malignancies encountered in the neonate. It involves the peripheral nervous system originating from the neural crest cells, and the prognosis is poor due to frequent metastatic disease. It is therefore of capital importance both to understand better the etiology of the disease and to improve screening. For the time being, screening identifies mostly early onset and self-limited tumours, a number of which have the ability to regress spontaneously [4]. Although genetic factors are considered to play an important role in the occurrence of malignant tumours in infants, environmental exposures may also be involved. According to Narod et al. [25], a clear genetic basis has to date been established only for a small minority of childhood cancers. Therefore, there is considerable room for a potential etiologic role of environmental exposures.

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Until recently, sparse data were available on this topic. However, two recent papers drew attention to a possible impact of maternal hormonal treatment during pregnancy on the occurrence of neuroblastoma [20,23]. This prompted us to report here a case of neonatal neuroblastoma after *in utero* exposure to progestagens.

## 2. Case report

In a family with no known history of cancer in close relatives, a 25 year old non-smoking primigravida woman experienced vaginal bleeding at 15 weeks of amenorrhea. She was treated with 20 mg per day of dydrogesterone (a synthetic progestagen marketed as Duphaston®) and 2 tablets per day of Veliten®, a combination of a capillary stabilizing agent and vitamins C and E. Rest was prescribed as well with cessation from work for two weeks. The treatment was maintained until the 31st week of amenorrhea when the appearance of uterine contractions led to hospitalization. Ultrasonography showed that the foetus was normally developed for his gestational age and the mother's pregnancy weight gain was 9 kg. No clinical anomalies were found except for the persistence of uterine activity as well as a slightly incompetent cervix. Treatment was intensified with, in addition to Duphaston®, a prescription for an inhibitor of uterine contraction containing hydroxyprogesterone, progesterone and tocopherol (Tocogestan®) in a dose of 2 tablets/day for 5 days along with vitamin B6 (Magne B6®) and oxazepam (Seresta®) in a dose of 45 mg per day for 5 days. Evolution was rapidly favorable and the mother was discharged home with Tocogestan®, Seresta® and Magne B6®.

Delivery occurred at 40 weeks by forceps. The child was a boy of 3650 g. He was not breastfed.

A well-limited, painless mass of homogeneous consistency of approximately $5 \times 3$ cm was palpated on the fourth day of life in the left flank. Abdominal ultrasonography and CT scan revealed a retroperitoneal heterogeneous and well-delineated mass with calcifications. Its dimensions were $6 \times 4.5 \times 3.5$ cm, and it was adherent and pushing back the anterior wall of the left kidney that was slightly laminated. There was no locoregional extension to retroperitoneal nodes, kidney, vena cava or distal extension to the liver (according to ultrasonography and biological parameters), no invasion of the lungs (according to X-ray examination), and no skeletal involvement (as assessed by scintigraphy and myelogram). Diagnosis of neuroblastoma was suspected in view of the high levels of vanillyl mandelic acid (VMA) at 27.5 $\mu$mol/mmol of creatinine (normal value below 12) and of homo vanillic acid (HVA) at 24.5 (normal value below 20). Serum enolase was normal.

At 7 weeks of age a stage I left adrenal neuroblastoma was completely excised, leaving the kidney and its vascularisation intact. Liver, peritoneal or lomboaortic metastases were ruled out by visual inspection. Pathological examination confirmed the free margins of excision. After surgery, the VMA decreased to 11.9, i.e., at the upper limit of normal values, and HVA to 8.1. The dopamine level was normal at 153 nmol/mmol of creatinine (for a normal value below 550), as was the enolase. The child is now 9 years old and well.

## 3. Discussion

Our knowledge of the pathogenesis of neuroblastoma is poor. Identification of risk factors would substantially improve the control of the disease, and may lead to possibilities of primary prevention. Genetic predisposition is supported by the observation of rare familial aggregation of cases [28,29], reports of

a few cases with constitutional chromosomal anomalies [7,9], and an excess of neuroblastomas in neurofibromatosis [25] and possibly other genetic diseases [26]. Association with other conditions such as Beckwith–Wiedemann syndrome and to a lesser degree Hirschsprung disease has been reported but the causal or chance nature of the association remains under discussion [21]. However, these cases only represent a small proportion of all neuroblastomas, as confirmed by a large epidemiologic investigation concluding that there is a clear genetic basis only for a small minority of childhood cancers [25], and also by a study of concordance of childhood cancer in twins suggesting that there is no strong constitutional genetic component in cases other than retinoblastoma [2]. It should be noted that the only concordant pair in that study was 4 months old at diagnosis. In a review of the literature, concordance was described as more frequent in infancy [18]. In a report of a concordant pair of twins with neonatal and two months of age occurrence of neuroblastoma, *in utero* exposure to a beta-adrenergic agent was noted as well [19]. Genetics may thus play a role, especially in cases occurring early in life, but environmental factors, including *in utero* exposure, cannot be ruled out. Since the peak incidence of this disease is below the age of 2 [26], pre and perinatal events are important.

Current knowledge on the role of pregnancy characteristics, and/or environmental exposures of parents, is limited. The possible role of environmental as well as parental occupational exposure to radon [38], electromagnetic fields [36], pesticides and herbicides [17,22], metal fumes, benzene and asbestos [27] has been stressed. Case reports of neuroblastoma in fetal alcohol syndrome [13,34], including one infant also exposed to hydantoin [34], suggested a role for *in utero* exposure to alcohol, also found in a case-control study showing an increased risk for frequent alcohol consumption as well as for maternal hair dyeing during pregnancy [16]. Another study found an increased risk for maternal smoking [33]. Among drugs, only a few classes of compounds have been suggested as risk factors if consumed during pregnancy: they include diuretics, antiemetics and neurally active drugs [16,33]. Specific mention must be made of *in utero* exposure to phenytoin and its possible association with neuroblastoma [1,5,6, 15,32,34,35]. Several authors have noted the preferential occurrence of neuroblastoma among children affected by the fetal hydantoin syndrome [1,5,6,34,35]. The direct involvement of the drug in the fetal hydantoin syndrome is well recognized, but its responsibility in the causation of this neoplasm is still controversial.

The last class of therapeutic drugs possibly involved in neuroblastoma is sex hormones. The hypothesis of a role of progestagens was given attention recently by Mandel et al. [20], who described in the same institution three neuroblastomas in infants exposed *in utero* to progestagens. They noted an early onset of the tumours in these infants. A few years before this, Kramer et al. [16] had reported an increased risk of neuroblastoma with exposure to sex hormones prior to or during pregnancy. More recently, in a large case-control study, Michalek et al. [23] strongly supported the hypothesis of a link between hormones and neuroblastoma. The authors found, for any use of sex hormones during pregnancy, a relative risk as estimated from the odds ratio (OR) of 3 (95% CI: 1.3–6.9), going up to 4.4 (1.5–13.3) among boys and with a very strong risk for hormone use related to infertility at 10.4 (1.2–90.0). Another case-control study did not find such a statistically significant risk [33] with, however, an indication for a higher risk if the study was limited to cases of age up to one year (OR = 1.5) as compared to the whole population of cases (OR = 1.2). This is supported by Mandel et al. [20] who reported that out of 8 neuroblastoma cases below 1 year of age, 4 followed hormone-induced or treated pregnancies whereas only one out of 16 older cases had been similarly exposed to progestagens. In addition, Carlsen [3] reported another young child born from a mother who had received progesterone because of bleeding in early pregnancy as did White [39] in a case involving induction of ovulation and use of progestagens, and Milanesi in a case where human gonadotrophic hormone had

Table 1
Neuroblastoma after *in utero* exposure to progestagens

| Authors | Year of publication | Stage of neuroblastoma | Age at diagnosis | Sex | Description of exposure to progestagens | Other characteristics |
|---|---|---|---|---|---|---|
| Carlsen | 1996 | III | 7 months | Boy | Progesterone for bleeding during early pregnancy | |
| Mandel et al. | 1994 | IV-S | 5 months | Boy | Allylestrenol (Gestanon ®) for habitual abortions | Chorionic gonadotrophins (Chorigon®) |
| | | IV | 4 months | Boy | Allylestrenol (Gestanon®) for first trimester bleeding | |
| | | II | 6 months | Girl | Dihydroprogesterone for first trimester bleeding | Clomiphene citrate for anovulation |
| White et al. | 1990 | II | 13 months | Girl | Hydroxyprogesterone (Proluton®) | Mother 25 years of age with past history of 2 ectopic pregnancies. Induction of ovulation by Clomiphene |
| Sasco et al. | (present case) | I | neonatal | Boy | Progesterone (Duphaston®) for vaginal bleeding at 15 weeks of amenorrhea until 31st week, at this time the treatment was intensified with Tocogestan® | Mother 25 years of age, pregnant for the first time. Other therapies: Veliten®, Seresta®, Magne B6® |

been given in pregnancy [24]. All cases of neuroblastoma occurring after *in utero* exposure to progestagens are presented in Table 1 and cases following unspecified exposure to sex hormones are listed in Table 2.

Another interpretation of the results is suggested by a large case-control study including 1268 cancer cases extracted from the Swedish Cancer registry and twice as many controls identified through the Medical Birth Registry [8]. The authors examined pregnancy and delivery characteristics of women whose infants later developed an infant or child cancer. This included neuroblastomas but did not separate out that group. The general outcome of this study was negative, but some associations were found between pregnancy complications and childhood cancer. In spite of not being significant, associations with threatened abortion (OR = 1.8, 95% CI 0.8–4.2) or primary weak contractions (OR = 1.4, 95% CI 0.9–2.2) are noteworthy. Threatened abortions were described as being associated with childhood malignancy as early as 1958 [37], but the numbers involved were very small. In the Swedish study, the sample was large but the association not significant. As gestagens have not been used in Sweden for vaginal bleeding or uterine contractions since the 1960s [11], no hormonal treatment can be suspected as being at the origin of the increased ORs, but some sort of disturbed hormonal status may be a risk factor for both threatened abortion and child cancer.

An increased risk has also been found for induced pregnancies in a case-control study [23], in a study based on a national register for assisted conceptions [39] and a cancer register [14]. Progestagens are prescribed to some but not all women who become pregnant after induction of ovulation.

The occurrence of congenital anomalies has been described among infants exposed *in utero* to sex hormones, and presenting with transposition of the great vessels, congenital heart anomalies and hypospadias [23], although this was not confirmed by others [11,12]. One hormone, diethylstilbestrol, was the first transplacental carcinogen demonstrated in humans, showing that fetal exposure may result in tumour initiation, though the time of appearance is delayed until the second or third decade of life [10].

Table 2
Neuroblastoma after *in utero* exposure to other or unspecified sex hormones: main results

| Authors | Year of publication | Study | Description of exposure | Main results |
|---|---|---|---|---|
| *Case-control studies* | | | | OR 90% CI |
| Kramer et al. | 1987 | 2 sets of controls: random digit dialing; siblings; 1 to 1 matching | Sex hormones | |
| | | | 3 months prior to pregnancy | 2.5 0.98–6.40 |
| | | | 3 months prior to or during pregnancy | 2.3 1.11–4.44 |
| | | | During pregnancy | 1.8 0.73–4.45 |
| | | | During pregnancy | |
| | | | Provera® | 3 case mothers/1 control mother |
| | | | Birth control pills | 3 case mothers/1 control mother |
| | | | Sex hormones, unspecified | 4 case mothers/3 control mothers |
| | | | | OR 95% CI |
| Michalek et al. | 1996 | Controls from live birth certificate registry; 2 to 1 matching | Sex hormones | 3.0 1.3–6.9 |
| | | | for infertility | 10.4 1.2–90.0 |
| | | | for vaginal bleeding | 2.1 0.5–8.3 |
| | | | to maintain pregnancy | 1.3 0.4–4.0 |
| | | | for previous miscarriages | 4.1 0.4–45.5 |
| | | | Among boys and girls | boys girls boys girls |
| | | | sex hormones exposure | 4.4 1.7 1.5–13.3 0.4–6.3 |
| | | | infertility | 8.4 $\infty$ 0.9–76.5 1 case/0 control |
| | | | diagnosed early in life | 3.0 0.3 0.7–12.2 0.03–2.8 |
| Schwartzbaum | 1992 | Controls: other childhood cancers; about 7 controls per case | Sex hormones | OR 95% CI |
| | | | overall | 1.2 0.6–2.3 |
| | | | miscarriage or stillbirth | 1.9 0.6–5.8 |
| | | | children $\leqslant$ 1 year | 1.5 0.4–5.3 |
| *Other studies* | | | | |
| Kobayashi et al. | 1991 | Cancer registry | Maternal ovulation induction | 4 cases of neuroblastoma ($p < 0.001$) |
| Mandel et al. | 1994 | Hospital series | Pregnancy induced by hormone or pregnancy treated by hormones in the first trimester | 24 cases of neuroblastoma:<br>– 16 after 1 year of life, 1 case mother treated by progestatives<br>– 8 before 1 year of life, 4 (3 boys and 1 girl) case mothers treated by sex hormones including 3 by progestatives |
| Milanesi et al. | 1983 | Case report | Pregnancy treated by human chorionic gonadotrophin from 2 to end of 4 month | Neuroblastoma at the age of one month |
| White et al. | 1990 | Children born after *in vitro* fertilisation between 1985–87 | *In vitro* fertilisation or ovulation induction with clomiphene and artificial insemination | 5 cases of tumours:<br>– 3 neuroblastomas<br>– 1 medulloblastoma<br>– 1 supratentorial primitive neurectodermal tumor |

OR: odds ratio; CI: confidence interval.

By contrast, in experimental animals, *in utero* exposure results in a much earlier occurrence of tumours. Among primates in particular, the neonatal or early appearance of tumours can be explained by the length of the gestation period and the villous hematochorial configuration of the placenta [31]. In humans, the risk of gonadal germ-cell tumours has been related to *in utero* exposure to hormones [30]. Neonatal occurrence of neuroblastoma after phenytoin exposure is suggestive of a potential, rapidly acting transplacental carcinogenic effect.

Despite the recognition of the fact that neuroblastoma is the most frequent solid tumour in the first year of life and also that treatments with progestagens in pregnancy are common in several countries, therefore potentially leading to a purely co-incidental association, some arguments in favour of a causal link come from the few epidemiological studies validly assessing this association. Additional physiopathological considerations, and results from experimental studies further reinforces the need to explore this issue in more detail. The case we describe here provides new information as this is, to our knowledge, the first neonatal neuroblastoma described after *in utero* exposure to progestagens in a non-induced pregnancy. As cancer is a multifactorial disease, the association between a drug and a tumour, if real, will most probably be influenced by genetic susceptibility.

## 4. Conclusion

Further development will only come from an in-depth identification and evaluation of the interactions between suspected or proven carcinogens and specific traits of the genetic background. In the meantime, it would be prudent to avoid the prescription of hormones during pregnancy. Faced with a case of neuroblastoma, especially in view of its early appearance and its occurrence in a male infant, it is important to document carefully exposure during pregnancy to exogenous influences, including that to sex steroid hormones. Finally, in the present context of screening having not yet demonstrated its efficacy in the general population of all infants, and considering the poor compliance observed in some countries, efforts could be made to ensure focused investigation of infants born following induced pregnancy or whose mothers have experienced threatened abortion and/or exposure to progestagens during pregnancy.

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