SHORT COMMUNICATION

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Etiological aspects of congenital diaphragmatic hernia: results of a case comparison study

Abstract We report the results of a parental questionnaire concerning possible etiological and teratological factors, such as exposure to herbicides, in the development of congenital diaphragmatic hernia (CDH). The herbicide Nitrofen interferes with lung development in rats, can induce diaphragmatic hernia and greatly resembles thyroid hormone. No association with the studied teratogens nor with maternal thyroid dysfunction was found. The questionnaire was completed by 33 parents whose baby had CDH, and by 43 couples whose baby had oesophageal atresia. The resemblance of Nitrofen to thyroid hormone, a well-known growth factor for the developing lung, is of particular interest from a pathogenetic point of view in the development of CDH.

Introduction

Congenital diaphragmatic hernia (CDH) is a serious malformation characterized by a diaphragmatic defect and bilateral lung hypoplasia (Areechon and Reid 1963). In the Netherlands its incidence is estimated at 1 in 3000 liveborns. Despite recent changes in therapeutic approach, its mortality rate still amounts to 40%.

The etiology of CDH in the human newborn remains largely unknown (Cunnif et al. 1990), but in animal mod-

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els several teratological processes including exposure to chemicals have been found to induce CDH (Cullen et al. 1985). The present study was undertaken because within a few months five newborns from a circumscribed area with heavy industry and intensive agriculture and market gardening were admitted with CDH. In these areas fertilizers and herbicides are extensively used.

In this study we report the results of a parental questionnaire concerning possible etiological and teratological factors in the development of CDH.

Patients and methods

The Sophia Children's Hospital is a tertiary referral hospital that serves a region with a population of ± 3 million inhabitants, and an annual birth rate of approximately 35 000 newborns. We approached all parents of children with a posterolateral CDH ($n = 48$) admitted from 1985 to 1991; stillborns were excluded. Patients with an oesophageal atresia (EA) served as a control group ($n = 66$). After giving their consent the parents received a questionnaire, consisting of 72 items. Questions were asked related to potential teratological data: marital status, family planning, contraception, treatment for delayed fertility, complications, illnesses and medications during gestation, way of delivery, occupation and social class, drug abuse alcohol abuse, smoking, X-rays, and exposure to occupational and environmental chemicals. Reference lists were included with the names of 42 commonly prescribed drugs and 40 chemicals (Addenda I and II). Statistical analysis was based on chi-square analysis of contingency tables. Statistical significance was accepted at the $P < 0.05$ level.

Results and discussion

The final study group consisted of 33 couples (response rate 68%) whose baby had CDH, and 43 couples whose baby had EA (response rate 65%). Mothers of newborns with EA showed a higher incidence of polyhydramnios and subsequently more ultrasound examinations, hospital admissions, and hospital deliveries. The incidence of ovulation induction procedures and spontaneous abortions in EA mothers was higher than in CDH mothers. The number of prescribed medications during pregnancy was higher in fathers and mothers (in the first month of pregnancy

only) of CDH newborns. The type of drugs taken ranged widely and no specific association was found to be significant. The incidence of exposure to occupational and environmental chemicals did not differ between groups. Etiological studies in Hungary on isolated EA compared with normal controls also failed to show an association with studied teratogens (Szendrey et al. 1985).

The herbicide Nitrofen (2,4-dichlorophenyl-p-nitrophenyl ether) is an agent with a strong teratogenic potential that in rats interferes with lung development resulting in bilateral lung hypoplasia and induction of anatomical malformations including diaphragmatic hernias (Manson 1986). The stereochemical configuration of Nitrofen greatly resembles that of triiodothyronine (T_3) and thyroxine (T_4). Thyroid hormone is a well-known trophic factor for normal lung development and alveolar cell differentiation (DeMello et al. 1989). Moreover, maternal hypothyroidism has been associated with an increased risk of a variety of birth defects in offspring (Potter 1980; Khoury et al. 1989), but information on its role in CDH is lacking. The exact mechanism of teratogenesis is not known but evidence is accumulating that Nitrofen may interact with the embryonic nuclear receptors for thyroid hormone (Manson 1986).

This hypothesis links pulmonary hypoplasia and CDH with thyroid hormone status, and consequently, congenital defects with maternal thyroid disease. None of the mothers from either group suffered clinically from chronic thyroid dysfunction. These findings do not support the hypothesis that maternal hypothyroidism is a risk factor for the development of lung hypoplasia or CDH. To enable further research into the etiology of CDH, the actual moment of maldevelopment should be defined first: absent closure of the diaphragm and subsequent pulmonary hypoplasia, or an alternate pathogenetic mechanism with primary poor development of the lung bud and subsequent delay of closure of the pleuroperitoneal membrane, as has been suggested by Iritani (1984). The role of thyroid hormone status and that of thyroid hormone receptors in lung tissue and their relation with the development of lung hypoplasia in fetuses with CDH remains to be elucidated.

In conclusion, no etiological factors could be identified that are associated with either the development of CDH or EA. Although chemically induced birth defects account for only 5% of birth defects observed in the population (Wilson 1977), it remains worthwhile to identify potentially hazardous chemicals in the environment in order to minimize the risk of congenital malformations.

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Addendum I

List of drugs

Agiolax®, Semen Plantaginis Ovatae, Fructus Cassiae; Agrégola®, Cetylpyridinium Chloride; Algesal®, Diethylaminesalicylate; Antrenyl®, Oxyphenonium Bromide; APC®, Acetylsalicylic Acid, Caffeine, Paracetamol; Ascal®, Carbasalate Calcium; Augmentin®, Amoxycillin, Clavulanic acid; Bactrimel®, Trimethoprim, Cotrimoxazole; Broxil®, Pheneticillin; Buscopan®, Hyoscine Butylbromide; Canesten®, Clotrimazole; Clamoxyl®, Amoxycillin; Coldrex®, Acetylsalicylic acid, Phenylephrine; Daktarin®, Miconazole; Davitamon®, Vitamin A-B-E; Dolviran®, Acetylsalicylic Acid, Caffeine, Codeine; Dulcolax®, Bisacodyl; Duphalac®, Lactulose; Eryfer®, Ferrous sulphate; Fero-Gradumet®, Ferrous sulphate; Ferumat®, Ferrous fumarate; Finimal®, Paracetamol; Caffeine; Flagyl®, Metronidazole; Fortral®, Pentazocine; Gaviscon®, Sodium alginate, Sodium hydrogenocarbonate; Glifanan®, Glafenine; Gynodaktarin®, Miconazole; Hedex®, Paracetamol; Metamucil®, Plantago ovata; Mogadon®, Nitrazepam; Nizoral®, Ketoconazole; Noctamid®, Lormetazepam; Normison®, Temazepam; Seresta®, Oxazepam; Valdispert®, Valerian; Valium®, Diazepam

Addendum II

List of herbicides

Actor®, Paraquat-diquat; Actril®, Ioxynil; A.U.MCPA®, MCPA; Baycor anti-yeast agent, Bitertanol; Birlane®, Chlorfenvinphos; Bladafum®, Sulfotep; Curator®, Carbofuram; Dedevap®, Dichlorvos; Folimat®, Omethoate; Gusadeen®, Azinphosmethyl/propoxur; Lannate®, Methomyl; Mesurol®, Methiocarb; Nitrofen®, Dinitrophenyl ether; Peropal®, Azocyclotin; Pirimor®, Pirimicarb; Ridomil®, Metalaxyl; Safrotin®, Propetamphos; Tamaron®, Methamidophos; Telone®, 1,3-dichlorpropene; Thiovit®, Sulphur; TMTD®, Thiram; Topsin®, Thiophanate-methyl; Torque®, Fenbutatinoxide; Trimaton®, Metamsodium; Vitigran®, Copperoxychloride; Dinoseb; Zineb; Formothion; Endosulfan; Phosphamidon; Zineb