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Possible altered mineral metabolism in human anencephalic fetuses

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Abstract

Neural tube defects are congenital abnormalities caused by failure of the neural tube to close during embryogenesis. We investigated trace elements (zinc, copper, manganese, cobalt, nickel, molybdenum, cadmium), livers, pancreata, sciatic nerves, diaphragms, and kidneys collected at autopsy from 33 anencephalic fetuses and 22 control fetuses. Collections were done on the right side using a titanium scalpel, plastic forceps, and acid-washed materials. Samples were wet ashed and analyzed using inductively coupled plasma mass spectrometry. The gestational age and birth weight (mean ± SD) of anencephalic fetuses were 25.8 ± 8 weeks and 729 ± 879 g, respectively; those of control fetuses, 28 ± 8 weeks and 1340 ± 1216 g, respectively. Liver concentrations (ppm, dry weight, mean ± SEM) of Zn (1075 ± 56 vs 668 ± 75; $P = .001$) increased in anencephalic fetuses, suggesting defective transport of Zn. Whether this is part of the cause of neural tube defects or a result of the disease is unclear.

Keywords: Neural tube defects; Zinc; Cadmium; Human fetus

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1. Introduction

Neural tube defects (NTDs) are congenital abnormalities caused by failure of the neural tube to close during embryogenesis [1,2]. Two common manifestations are spina bifida and anencephaly. Anencephaly, a striking abnormality in which there is virtual absence of the forebrain and the skull vault, always results in perinatal or neonatal death. The etiology of NTD appears to be multifactorial with a genetic component and a substantial environmental component [2]. Newfoundland, Canada, has a very high rate of NTDs (3.1/1000 live births, about half of these being anencephalic [AN] [3-5]). This rate is higher than rates in other areas in Canada, Scandinavia, England, and Wales and is almost as high as rates in urban Ireland, which has one of the highest rates in the world [6]. The incidence in Canada increases from west to east [7].

The exact mechanism for NTDs is unknown. Although there is a well-known association between folic acid deficiency and NTDs, fortification of flour with folate has not eliminated all NTDs [4]. Several reports have linked tissue zinc and cadmium concentrations with NTD or malformations of the central nervous system in both animals [8,9] and human beings [10-14]. We hypothesized that Zn and Cd contents of AN tissues would differ from those of control (CON) tissues. Therefore, the purpose of this study was to analyze the mineral content of selected tissues from autopsied AN and CON fetuses.

2. Methods and materials

2.1. Subjects

Samples of liver, kidney, diaphragmatic muscle, sciatic nerve, and pancreas were collected at autopsy from 33 AN fetuses and 22 CON fetuses. Control fetuses were term and preterm infants whose tissues had undergone minimal autolytic changes. All but 2 AN fetuses were stillborn and only 2 CON fetuses were stillborn. All tissues were collected from 6 different hospitals in 3 different regions of Canada (Newfoundland, Nova Scotia, and Ontario) with parental consent, after approval of the protocol by each institutional committee.

2.2. Tissue collection

All tissues were collected in a standardized procedure from the right side of the fetus. For approximately half the fetuses, the whole organ was collected after necessary tissue was removed for histopathological examination. For the remaining fetuses, only part of each organ was available. Tissue was rinsed with deionized water, subsequently patted dry with paper toweling to remove excess blood, and placed in labeled acid-washed containers. Tissue was cut using titanium knives, made in-house, and plastic forceps and then placed in the freezer at $-70^{\circ}C$ until analysis. Not all tissues were available from each subject.

2.3. Sample preparation and analysis

Thawed samples were weighed, freeze-dried, reweighed, and then digested with nitric acid using PARR microwave digestion bombs (PARR Instrument Co., Moline, IL) and a standard microwave oven [15,16]. Samples, certified controls (NBS oyster tissue #1566 and NBS