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Today's epidemics in children: Possible relations to environmental pollution and suggested preventive measures

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Abstract

Background: Facts and hypotheses on the relationship between some children's diseases or disorders and external stressors during the developmental stage of a child, both prenatally and postnatally are described in literature. In this paper the following changes in patterns and causes of the main childhood illnesses are summarized and recommendations for actions are made.

- Prematurity
- Intra-uterine growth restriction
- Testicular dysgenesis syndrome
- Type I and Type II diabetes
- Asthma, atopy and hay fever
- Autism
- Attention deficit hyperactivity disorder (ADHD)
- Learning disabilities
- Cancer
- Obesity
- Hearing problems

Results: Literature provides a growing amount of information on changing patterns in childhood diseases.

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Conclusions: The following recommendations for action are formulated:
- Immediate research on endocrine disrupters in relation to prematurity
- Diabetes: avoid Maillard Compounds in liquid baby food and in food in general: promote breastfeeding
- Asthma: avoid exposure to smoking, the use of chemical household products, dioxin and dioxin-like chemicals, and avoid air pollution with high levels of particulate matter, especially around conception, during pregnancy and in the first years of life
- Autism: more research on incidence and causes
- ADHD and learning disabilities: more research on prevalence and causes. Preventions: 1) preconception counselling to avoid potentially harmful substances; 2) controlling and further lowering levels of polychlorinated biphenyls, lead and methyl mercury
- Cancer: promote breastfeeding, carry out research into effects of foetal exposure to internal fission-product radionuclides
- Obesity: stop smoking in pregnancy, avoid parental obesity, longer night sleep
- Hearing problems: lower noise levels in discothèques, promote the day-evening-night level to avoid noise (longer night sleep)

Key Words: *Children, environment, health, epidemic*

Introduction

Health problems in children that are related to environmental contaminants may follow from developmental disturbances in intra-uterine life or in the first years of life. This article describes facts and hypotheses on the relationship between some children's diseases or disorders and external stressors during the developmental stage of a child, both prenatally and postnatally. During growth and development the organs of children may be affected by exposure to harmful environmental stressors. The first trimester of pregnancy is a period of organogenesis. Disturbances due to exposure to agents that damage or control the morphology of developing tissue can for example cause hypospadias and gastroschizis, obesity, or autism. Learning disabilities and attention deficit hyperactivity disorder (ADHD), and trans-sexuality may be caused by interference during the second trimester, prematurity in the second and third trimester and intra-uterine growth retardation and cancer in all three trimesters of pregnancy. Diseases related to autoimmune phenomena such as type I diabetes, and to allergic diseases such as asthma and hay fever might have their roots in pregnancy, but the first year(s) of life are important as well, which also seems to be the case for ADHD. These developmental effects can follow from intrinsic subtle heritable genetic or genomic disturbances or from hormonal or hormone-mimicking exposures.

Socioeconomic factors have an influence on every stage of a child's life. Therefore, socioeconomic disparities have to be considered in the relationship between environmental exposures and children's health. A brief overview of the impact of social inequalities is given in a separate contribution to this supplement, entitled 'Children's environmental health: why should socio-economic disparities be considered?'

Prematurity

There has been a rise in prematurity in the last decade. Eight percent of all deliveries are premature, which means about 500 000 in Western Europe each year. Prematurity is an important public health problem with health consequences later in life. Emotional costs for the individual mother and hospital costs for society are high for every case of prematurity. It is well known that socioeconomic factors can play an important role [1]. A 40% increase in prematurity in the last decade in the north of Belgium (Flanders) cannot be explained by changes in the four most well known determinants such as multiple pregnancies, obstetric interventions such as early caesarean sections, the use of assisted reproduction techniques, or maternal age [2]. An increase is also seen in many developed countries including France [56], USA [57] and Canada [58]. An effect on the neuro-endocrine axis, resulting in a lower progesterone level, is hypothesized to be a risk factor. This is supported by animal experiments[3]. It is plausible that this increase in prematurity is the female counterpart of the testicular dysgenesis syndrome and may be caused by endocrine disrupting chemicals (EDCs) (see below), or by direct effects of exogenous hormone-like substances such as phthalates during the pregnancy [4]. Prevention of what triggers premature delivery is very important.

To clarify this it is recommended to monitor endocrine disrupting chemicals (EDCs) in pregnant women with a threat of premature delivery and in their mothers (analogous to the DES story). This research should also be carried out in different regions of Europe and these regions must be directly involved in research and hypothesis formulation.

Intra-uterine growth restriction (IUGR)

Intra-uterine growth restriction (IUGR) is a pathological decrease in the rate of foetal growth resulting in a

foetus that does not achieve its intrinsic growth potential [5]. Another definition is all babies with a birth weight below the 10th percentile for gestational age and sex [59]. Many pollutants (including smoking, alcohol, drugs and medicines) used by the mother or accumulated in her body fat can negatively influence growth of the baby. IUGR can contribute to adult diseases such as cardiovascular diseases, diabetes, renal diseases, disorders with high blood pressure, high triglycerides and high cholesterol. Thus, some of these adult diseases may have a foetal origin [6]. Both abnormal foetal programming and anatomical changes in the foetus can result in disease later in life. Negative effects on blood pressure in later life might also be based (besides effects of an anatomical change in vasculature) on a disturbance of the cortisol/cortison ratio. This ratio may be influenced by the inhibition of 11 beta-hydroxysteroid dehydrogenase type 2 in the placenta by pesticides or organotins resulting in higher cortisol levels in the baby [7,8]. IUGR babies are often born prematurely. In a retrospective study on a group of growth retarded babies with birth weights over 1500 g but under the tenth percentile, in relation to gestational age 35% have an unknown cause of the growth retardation [25].

Studies from the Czech Republic have shown an impact of particulate matter on IUGR in a highly polluted area. Mothers who were exposed to particulate matter (PM10) annual levels above 40 $\mu g/m^3$ or annual PM2.5 (particles smaller than 2.5 mm) levels above 27 $\mu g/m^3$ during the first month of gestation had a significantly increased risk of giving birth to a child with IUGR [55]. Studies based on a four-year dataset showed similar results. The risk of IUGR was 1.44 higher (95% CI 1.03–2.02) in the group of mothers exposed to mean PM10 levels between 40 and 50 $\mu g/m^3$ compared to those exposed to mean PM10 below 40 $\mu g/m^3$ during the first month of gestation. Levels above 50 $\mu g/m^3$ increased the risk to 2.14 (95% CI 1.42–3.23) [34]. Further analysis showed a highly significant increase of IUGR with exposure to a range of carcinogenic polycyclic aromatic hydrocarbons (PAHs) above 15 ng/m^3. The adjusted relative risks were 1.59 (95% CI 1.06–1.39) for medium levels of carcinogenic PAHs and 2.15 (95% CI 1.27–3.63) for high exposure levels. Interestingly, all these effects were associated with exposure during the first month of gestation. Molecular epidemiology studies suggest involvement of various biological mechanisms affecting birth weight and IUGR. The available data do not allow precise identification of specific pollutants and the effect of the timing of exposure; thus more studies are warranted with specific focus on the carcinogenic PAHs.

Research on the association between IUGR and adult disease is needed. Further prospective studies with long-term follow-up are warranted in this group of babies.

Testicular dysgenesis syndrome

The increases in hypospadias, cryptorchidysm and testicular cancer and the decline in sperm count is hypothesized as part of the testicular dysgenesis syndrome [9,10]. Endocrine disrupting chemicals (EDCs) are blamed for possibly contributing to the increased prevalence of this syndrome during recent decades, together with life-style factors and genetic background. A very high percentage of hypospadias has recently been noted in a population based study from Denmark with a prevalence of 4.6% [11]. Foetal and placental growth impairment seem to share a pathogenetic factor with this abnormality, with an increased level of follicle stimulating hormone three months after birth in the babies with hypospadia which may indicate a shortness of testosterone.

Transsexualism

A combined female and male effect of EDCs on the offspring (possibly in combination with infection) is trans-sexualism. This disease also fits with the concept of endocrine disruption. Recently a rise was reported in Sweden by Olle Söder [12]. In addition, in the offspring of mothers on anticonvulsant drugs (phenobarbital) a significant increase in trans-sexualism has been found [13]. For action, see above under prematurity.

Type I and type II diabetes

In the last three decades there has been an increase in auto-immune diseases such as type I diabetes in young children. The prevalence of type I diabetes is about 1.5 per 1000 children. There is a shift in HLA-type; less HLA type: Dr3, Dr4 and more Dr3 or Dr4 alone.

Gillespie suggested that the increase of type I diabetes must be the result of exposure of a genetically susceptible subgroup of the population to an environment that is increasingly conducive to diabetes development: "The heightened proportion of lower risk haplotypes and decreased median age at onset of the disorder are suggesting an environmental contribution on diabetes development." [15] Interesting is the hypothesis that air pollution, especially ozone, plays a role in development of type I diabetes, because of oxidative damage to the beta cells in susceptible children [14]. Finland and Sardinia are known to have high prevalences of diabetes.

Type II diabetes in children is rapidly increasing and can be considered a new epidemic [16]. The increase in type II diabetes is assumed to be related to obesity; however, there are indications that type II is

also based on an auto-immune phenomenon. Both types of diabetes are aggravated by consumption of Maillard compounds (caramelized sugars and proteins present a.o. in liquid baby formula) [17–19]. Advanced glycated end (AGE) products or Maillard compounds are formed during cooking or container sterilization at 110–120°C during 10–30 min. Chips or French fries, crackers and crisp bread are known to be high in AGEs, as are some liquid baby formulas, due to sterilization. Breastfeeding protects against diabetes. Formula, on the other hand, contains a protein from cows that has been suggested to be involved in the development of type I diabetes. Dietary measures and increased activity can prevent or postpone the development of type II diabetes, see also below under obesity. Breastfeeding must be supported as a means for preventing diabetes development.

Asthma, atopy and hay fever

There is a steep increase in allergic diseases (allergic asthma, hay fever and atopic dermatitis) and atopy in many countries around the world. This is less clear for non-allergic asthma, but it is difficult to separate between the different causes of asthma and often the causes are mixed. In this section mainly the non-allergic mechanisms of asthma are discussed.

A sharp increase in asthma is described in the UK between 1970 and 1990, from 6% to 12%, as well as an increase in hay fever from 12% to 23%. This increase seemed to continue until the beginning of this century. In recent years it has levelled off to a stable but high level. Lung development hampered by intra-uterine growth retardation results in lung dysgenesis, making the baby susceptible to the development of asthma. A good example is given in the recent publication in JAMA by Maureen Hack, who found a 21% prevalence of asthma in children born with birth weights under 1000 g, while the prevalence in Cleveland, Ohio in normal birth weight children is 9% [20]. In several regions of Europe it is also 9%. Data from south-west Germany, however, are around 5%. This is partly explained by the tradition in Germany not to use the word 'asthma'. There is a sharp difference of incidence between Germany and the Netherlands which is probably due to medical diagnosis tradition. There is some levelling off described in Switzerland and Rome, Italy. In Germany the prevalence of hay fever (and the condition atopy) has stabilized at 35% [21,22].

A negative effect on lung development has been described in relation to in-utero exposure to smoking, dioxins [60,61], the use of different chemical household products by the mother [23] or air pollution especially the polycyclic aromatic hydrocarbons (PAHs) and volatile organic compounds (VOCs).

Also allergies are described more in hotspots with dioxin pollution, while atopy is related to smoking of the mother [24].

Prevention

A further reduction of exposure to smoking, the use of cleaning products containing synthetic chemicals, to dioxins and dioxin-like chemicals, and avoiding air pollution and VOCs around conception and during pregnancy as well as in the first years of life are important to reduce or at least control the prevalence of asthma.

Autism

An increase in prevalence of autism has been suggested. However, this might at least partly be explained by an increased awareness of autistic symptoms and a shift in diagnosis, and further studies of the incidence of autism are warranted [25]. A UK publication states that a seven- fold increase (0.3 to 2.1/1000) for autism was seen from 1988 to 1999. It has been reported that autism can be related to congenital rubella, as is the case with type I diabetes, and also to thalidomide when used at day 49 after conception [26]. This indicates that events occurring early in pregnancy can influence the development of the disease. For example, environmental chemicals which may influence the immune system may contribute to the ontogeny of an autoimmune process in a genetically susceptible foetus, possibly in combination with an infection such as a streptococcal infection. In line with this hypothesis, a higher prevalence of autoimmune diseases has been described in families of autistic children [28].

Research: The CHARGE (Childhood Autism Risks from Genetics and the Environment) study is a large ongoing case-control study of children with autism or developmental delays. A broad array of exposures and physiological factors are investigated to determine whether particular genes or environmental exposures are associated with symptoms (for details see http://beincharge.ucdavis.edu/).

Attention deficit hyperactivity disorder (ADHD)

The prevalence of attention deficit hyperactivity disorder has been suggested to be increasing. The prevalence of ADHD is high: 3–5% at school age of which 30–60% persists into adulthood. In Germany 1.6% of all children use methylphenidate, the most widely used pharmacological agent in ADHD treatment. A doubling of the use of this drug is described in the Netherlands from 1990 to 1995.

The genetic component of the disease is estimated at 80% and some of the genetic factors involved may

overlap with genes influencing autism and dyslexia. Gene-environment interactions are investigated, but no conclusive results have been reported yet [29]. Exposure to lead, PCBs, or nicotine during pregnancy are suggested to contribute to or cause the expression of the phenotype [30,31]. Brain abnormalities have been described in fronto-striatal, temporal and cerebellar volume in neuroimaging studies of children with ADHD. Unaffected brothers and sisters show the same cerebral abnormalities, but not the cerebellar abnormalities [32]. The cerebellum develops mainly after birth, and this might explain why a relation with postnatal exposure to manganese in drinking water and in bottle-feeding formulas has been reported.

Learning disabilities

Learning disabilities defined as an IQ lower than 70 are found in about 1–2.5% of children. Lead, methyl mercury, PCBs and dioxins are known intrauterine neurotoxicants suggested to cause a poorer cognitive development [25,26]. Co-exposure to more than one neurotoxic substance is thought to be important in this respect [33]. Examples of such 'Multiple Exposure' include PCBs, PBBs and dioxins with methylmercury and/or lead, and the combination of PCBs and dioxins. Other examples are combinations of different pesticides together, or particulate matter and polycyclic aromatic hydrocarbons (PAHs) acting together as in air pollution [34]. Life-style factors such as smoking, alcohol and drugs are other well known neurotoxicants [25].

Disturbed thyroid hormone metabolism in both the mother in early pregnancy and later in the developing child might have negative effects on cognitive development [35]. PCBs and other chemicals such as dioxins and PBBs, mercury, DDE, nanochlor and hexachlorobenzene can all have negative effects on thyroid hormone metabolism by lowering T3 levels in the mother. In the second half of pregnancy, when the baby starts to produce its own thyroid hormone, inhibited transport of T3 into the neuronal tissue can have negative effects for development [36–38].

Prevention

Learning disabilities and ADHD might in some cases be prevented by good preconception counselling at an individual level. Recommendations include folic acid supplementation, control of the thyroid hormone status, sufficient vitamin A and the use of food high in anti-oxidants such as broccoli, berries, tea, beets, carrots, olive oil and green vegetables and fish (small) [25]. Smoking and drinking should of course be avoided. At the level of government and industry, suggested actions include controlling and further lowering the levels of dioxins, PCBs, and other persistent bioaccumulating toxicants such as brominated flame retardants, musks, alkylphenols and also metals such as lead and mercury.

Cancer

Childhood cancer is rare, affecting about 1 in 10 000 children each year in Europe. In a recent article in the Lancet, Steliarova-Foucher et al. describe a 1.0% incidence increase per year since the 1970s for the last three decades in children (0–14 years) and 1.5% in adolescents. In particular, for infants the increase of 1.6% per year is significantly more than in the other age groups [39]. The most notable cancer in this age group is neuroblastoma [40,41].

A trend of an increase in brain cancer (1.5% increase annually) as has been reported in the USA has not yet been reported in Europe. This could be a result of better diagnostic facilities such as MRI. It is likely however that there is also a real effect which needs to be monitored by the use of the improved differential diagnosis of neurological childhood disease [43]. In the 1–4 years age group there has been a demonstrable increase in acute lymphoid leukaemia (ALL) of unknown aetiology. Most significant is a positive association with higher socioeconomic status (SES) [44]. Since childhood leukaemia rates have been found to be significantly increased near certain types of nuclear plants, exposure to radio-active fission product isotopes has come under suspicion as a cause. It is now universally conceded that exposure of the foetus to external ionizing radiation (e.g. X-rays) causes childhood cancer.

In order to improve prevention, breastfeeding longer than six months confers some protection against acute lymphoid leukaemia and should be encouraged.

Obesity

The recent epidemic in obesity in children is of great concern, because of the development of type II diabetes early in life as well as other problems associated with overweight. Factors during foetal life and life-style factors, such as less physical activity and more foodstuffs rich in saturated fats and sugars are blamed.

There are indications that factors during foetal life may also affect the appetite centre. The set-point of appetite is optimal for bad environmental circumstances but much too tolerant when food is abundantly present. It is known that conscripts conceived during the height of the Dutch Hunger Winter were exposed to malnutrition (mainly protein deficiency) during the first three month in utero. These conscripts were more obese than controls at age 19 years [45]. Also, later on at the age of 50 years, obesity was found

to be related to prenatal malnutrition [46]. It is unknown if other causes of intra-uterine growth retardation, such as pesticides or PCBs which interfere with the functioning of metabolizing enzymes in the liver and with lipid metabolism, may be related to obesity later in life. Leptin levels might give an answer in follow-up studies of cohorts studying effects of these pollutants.

The Avon Longitudinal Study of Parents and Children (ALSPAC) includes a long-term, prospective population-based study studying several aspects [23]. Data from the ALSPAC study show a significant relation between parental obesity (a.o.genetic factors), maternal smoking of more than 20 cigarettes a day during pregnancy, birth weight, TV viewing, shorter duration of night time sleep and catch-up growth between birth and two years and childhood obesity. However, childhood obesity has little effect on future economic, educational and social well-being [47,48]. The finding that smoking in pregnancy is related to obesity in childhood can indicate that other compounds causing oxidative stress can have the same effect.

Hearing problems

It has been estimated that approximately 10% of Europeans suffer from hearing loss [54]. Studies have shown that the proportion of young people with hearing impairment and symptoms of tinnitus is high [49–51]. Congenital hearing impairment affects 0.1% of all live- born children, but is 10 times higher in graduates of neonatal intensive care units [52]. Problems with hearing may result from damage in the perinatal period f.i. by bilirubin in preterm babies, or during intra-uterine life when exposed to high levels of PCBs [30].

Because young people have never been exposed to occupational noise, exposure to leisure noise is a likely explanation for the observed notch at 4–6 kHz in the audiograms, which is typical for a noise-induced hearing loss and tinnitus. Noise levels in discotheques, at rock concerts, from personal audio equipment, in entertainments, from toys and firecrackers can be extremely high and damaging to the ear. Hearing damage occurs either due to continuous and repeated noise over a long duration or due to high bursts of noise of short duration (e.g. impulse noise). Based on the risk damaging criterion which was derived from empirical studies in the occupational environment (ISO 1999), it has been estimated that 10–20% of young people may be at risk for noise-induced hearing impairment due to loud music [53].

Prevention: It is recommended that education of young people about the adverse effects of noise must be improved to make them more sensitive to the hearing issue, and to make them change their behaviour when exposed to loud sound sources of various kinds. The risk of hearing impairment due to loud music can be substantially reduced if average noise levels on the dance floor and at rock concerts is limited to at least below 100 dB(A). Nevertheless, even this value imposes a risk for frequent visitors. The use of portable audio equipment has increased throughout recent years due to digital recording and mass storage devices. Only devices that fulfil the recommendations of maximum sound levels according to EN 50332 [62] should be available on the market.

Summary actions

The following actions are recommended:

- Immediate research on endocrine disrupters in relation to prematurity
- Diabetes: avoid Maillard compounds in liquid baby food and in food in general. Promote breastfeeding
- Asthma: avoid exposure to smoking, the use of chemical household products, dioxin and dioxin-like chemicals, and avoid air pollution with high levels of particulate matter, especially around conception, during pregnancy and in the first years of life
- Autism: more research on incidence and causes
- ADHD and learning disabilities: more research on prevalence and causes. Preventions: 1) preconception counselling to avoid potentially harmful substances; 2) controlling and further lowering levels of polychlorinated biphenyls, lead and methyl mercury
- Cancer: promote breastfeeding, carry out research into effects of foetal exposure to internal fission-product radionuclides
- Obesity: stop smoking in pregnancy, avoid parental obesity, longer night sleep
- Hearing problems: lower noise levels in discotheques, promote the day-evening-night level to avoid noise (longer night sleep).

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