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Review article

Prenatal irradiation–induced brain neuropathology and cognitive impairment

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Abstract

Embryo/fetus is much more radiosensitive than neonatal and adult human being. The main potential effects of pre-natal radiation exposure on the human brain include growth retardation, small head/brain size, mental retardation, neocortical ectopias, callosal agenesis and brain tumor which may result in a lifetime poor quality of life. The patterns of prenatal radiation-induced effects are dependent not only on the stages of fetal development, the sensitivity of tissues and organs, but also on radiation sources, doses, dose rates. With the increased use of low dose radiation for diagnostic or radiotherapeutic purposes in recent years, combined with postnatal negative health effect after prenatal radiation exposure to fallout of Chernobyl nuclear power plant accident, the great anxiety and unnecessary termination of pregnancies after the nuclear disaster, there is a growing concern about the health effect of radiological examinations or therapies in pregnant women. In this paper, we reviewed current research progresses on prenatal ionizing irradiation–induced abnormal brain structure changes. Subsequent postnatal neuropsychological and neurological diseases were provided. Relationship between irradiation and brain aging was briefly mentioned. The relevant molecular mechanisms were also discussed. Future research directions were proposed at the end of this paper. With limited human data available, we hoped that systematical review of animal data could relight research interests on prenatal low dose/dose rate irradiation–induced brain microanatomical changes and subsequent neurological and neuropsychological disorders.

Keywords: Prenatal; Ionizing radiation; Neuropathology; Brain diseases

1. Introduction

Radiation research, in particular, low dose/dose rate radiation, becomes important nowadays than ever before due to the construction of more nuclear power plants worldwide to reduce energy shortage, increased hospital stockpiling of nuclear waste from medical diagnosis, the use of X-ray computed tomography (CT) (CT scan), isotopes for diagnosis, radiotherapy, occupational exposure and possible radiological terrorism. Human brain may be exposed to high (>100 mSv, such as A-bomb, radiological or nuclear incidents, nuclear power station accident, radiotherapy, etc) or low (<100 mSv, such as higher background, X-rays, CT, interventional medical exposures-fluoroscopically guided techniques, industrial radiation etc) dose/dose rate ionizing radiation [1–13]. The exposure may be acute, fractionated or chronic. Prenatal radiation exposure may have serious consequences for postnatal brain development at different stages of human life, including decreased brain

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size, mental retardation, seizures and epilepsy, behavioral alterations, brain cancer and aging [14–17]. It may also cause the great anxiety and unnecessary termination of pregnancies due to lack of knowledge of pregnant women [18]. Significant negative effects on the developing human brain have been reported among survivors of the atomic bombings of Hiroshima and Nagasaki exposed in the gestational period of 8–15 weeks [19,20]. However, negative effects of irradiation with different radiation doses/dose rates from single radiation sources in gestational periods are still lacking. In this paper, human epidemiological study of prenatal irradiation–induced brain pathological and subsequent cognitive impairment was presented. Systematical review of the effects of prenatal radiation exposure from preimplantation period to late gestational days was also performed. We hoped that animal experimental data could shed light on better understanding the effect of various sources of radiation exposure at different gestational days, and provide clues for further epidemiological study of the lifetime effect of single or multiple components of radiation exposure during different pregnancy periods.

2. Pre-natal ionizing radiation exposure and postnatal brain neuropathology and subsequent neuropsychological changes

2.1. Human study

2.1.1. Neuropathological changes

Human prenatal brain development has been generally classified into four periods from the day of ovulation, i.e., 0–7 weeks, 8–15 weeks, 16–25 weeks, and >26 weeks (Table 1). The rapid development of the human cerebral cortex occurs from 8 to 15 weeks after ovulation, and by 16 weeks, the normal number of neurons in the cerebral cortex of the adult human has been achieved [21]. During the preimplantation period, radiation exposure at $\geqslant$0.5 Gy causes death of the embryo [22]. X-rays irradiation with about 1 Gy prior to gestational fifth month induces neonatal malformation (34%), particularly microcephaly and reduces cranial circumference [23]. Epidemiological studies of A-bomb survivors with abnormal neuronal migration and small head size indicate that 83% of them are prenatally exposed to radiation >0.1 Gy at 8–15 weeks [20,24–28]. While it may still be debated, Down's syndrome and related abnormalities have been reported in those prenatally exposed to higher background radiation in the coastal Kerala population in India [29,30] and to fallout of Chernobyl reactor accident [31–33]. In the latter, neural tube defects and microcephaly are also observed after prenatal radiation exposure [34]. It is now generally accepted that no brain damaging effects may be observed in fetal exposure to 0.05 Gy at any period of gestation, and mental retardation may be induced by radiation dose of more than 0.1 Gy [35].

2.2. Neuropsychological changes

The neuropsychological effect of radiation exposure is also depending on the developmental periods and radiation doses (Table 2). Severe mental retardation has been reported in children prenatally treated with radium since 1929 [23]. At gestational 2–7 weeks, irradiation at >0.5 Gy induced neurological and motor deficiencies and growth retardation. At gestational 8–15 weeks, or early fetogenesis, high radiosensitivity exists for the development of the central nervous system. Irradiation at >0.05 Gy induced reduction in intelligence quotient (IQ) and incidence of severe mental retardation depending on dose [22]. Prenatally exposed survivors (exposed in the 8th through the 25th week) of the atomic bombings of Hiroshima and Nagasaki have severe mental retardation and seizure [20,24–28]. The threshold doses for severe mental retardation have been proposed to be 0.06–0.31 Gy between the eighth and the 5th weeks and 0.25–0.28 Gy between the 16th and the 25th weeks [19]. Subsequent study suggests a threshold dose of 0.5 Gy for prenatally exposed survivors with severe mental retardation [36]. Elevated mental disorders [37], speech-language disorders and emotional disorders [38] are also induced after prenatal exposure to Chernobyl reactor accident. Adolescents exposed to low-dose ionizing radiation in utero scores significantly lower in full-scale IQ than unexposed adolescents. The difference is restricted to verbal IQ and is not evident for nonverbal

Table 1
Pre-natal ionizing radiation exposure and neuropathological changes in the human.

Radiation periods	Radiation source	Radiation dose	Neuropathological changes	References
0–7 weeks	X-rays	$\geqslant$0.5 Gy	Embryo death	[22]
	X-rays	1 Gy	Neonatal malformation (34%), particularly microcephaly and reduced cranial circumference	[23]
8–15 weeks	A-bomb	>0.1 Gy	Abnormal neuronal migration and small head size	[20,24–28]
	Chernobyl nuclear power plant accident	15 times the normal permissible dose	Down's syndrome and related abnormalities, neural tube defects and microcephaly	[29–34]