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Thyroid Cancer in Children and Adolescents in Ukraine after the Chernobyl Accident (1986-1995)

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Abstract

The increase in the incidence of thyroid cancers in children and adolescents in Ukraine following the Chernobyl accident made it necessary to compile a clinical morphological register of respective cancers. In 1986-1994 there were 339 cases registered in children and adolescents, of them 211 children (who were operated at the age under 15 years) and 128 adolescents (who were operated at the age of 15-18 years). Before the Chernobyl accident (1981-1985) in Ukraine 59 cases of thyroid cancer in children and adolescents were reported: 25 cases in children and 34 cases in adolescents. This increase has been observed since 1990. In 1981-1985 the incidence rate (number of thyroid cancers per 100 000 children population) ranged 0.04 - 0.06. In 1990 this estimate was 0.23 and in 1992-1994 0.36 - 0.43, thus a 7-10 fold increase exceeding the pre-Chernobyl level. In the 5 most contaminated northern regions of Ukraine (Kiev, Chernigov, Zhitomir, Cherkassy, Rovno oblasts) and the city of Kiev the incidence rate was much higher. For example, in 1984 it was 3.8 in Chernigov oblast, 1.6 in Zhitomir oblast. The total "contribution" of the above-mentioned regions to the incidence of thyroid cancer in children after the Chernobyl accident makes more than 60%. It has been noted that in 1990-1994 there was an increase in the number of children operated at the age under 10, it means that these children were under 6 years at the time of the accident and were most sensitive to radioiodine exposure. As for the sex ratio, there has been a shift to males: in 1981-1985 F:M = 1.8:1, in 1990-1994 F:M = 1.4:1. Morphologically, 93.4% of 196 carcinomas resected from children and adolescents at the Institute of Endocrinology from 1986 to August 1st, 1995 were papillary carcinomas. They manifested high invasive and infiltrative growth, signs of intraglandular spread. Regional lymph node metastases were found in 59% of cases, distal lung metastases observed at various periods after surgery were noted in 23.7% of cases.

The increase in the incidence of thyroid cancers in children and adolescents in Ukraine following the Chernobyl accident made it necessary to compile a clinical morphological register of respective cancers at the major centre of endocrinology and endocrine surgery in Ukraine, Institute of Endocrinology and Metabolism in Kiev. This register includes all cases of thyroid cancer in patients who were under 18 years of age at the time of the Chernobyl accident. In the period of 1986-1994 there was a total of 531 such cases. There were 177 such patients operated at the surgical department of our Institute. The data on other patients are included into the register based on statistical information from 27 regions of Ukraine. In addition, we have developed an individual record form of clinical and morphologic data which includes the following: the duration of the disease, doses of radiation exposure, peculiarities of clinical course, surgical intervention, metastases, description of light microscopic and electronmicroscopic pathology. The compilation of a number of findings in each case for an extended length of time will allow for improved future analysis of the accumulated data [1].

This report will review the cases of thyroid cancer in Ukraine in children and adolescents aged 0-18 years at the moment of surgery. During the 5 years preceding the accident a total of 59 cases of thyroid cancer were registered in this age group, while during the period of 1986-1994, 339 additional cases were discovered. Between 1981-1985 the average number of thyroid cancer cases per year was 12. Following the Chernobyl accident between 1986-1990 there was an average of 22 cases per year. During the 1991-1994 period this number jumped to 57 cases per year.

In the group 0-14 years of age at surgery the number of new cases was the highest. In the 1981-1985 period there was a total of 25 cases of thyroid cancer among children in Ukraine whereas in 1986-1994 they numbered 211 cases. The most significant increase was observed beginning from 1990 : in 1990 : 26 cases, in 1991 : 22 cases, in 1992 : 47 cases, in 1993 : 43 cases and in 1994 : 39 cases. By August 1st, 1995, at the Institute of Endocrinology alone 29 children under 15 were operated, i.e. no decrease in the number of thyroid cancer cases can be anticipated.

Analysis of thyroid cancers in adolescents, who were operated at the age of 15-18 years showed that in the period of 1981-1985 34 cases of thyroid cancers were found, while in 1986-1994, 128 cases were found. Although it was more pronounced in the younger groups, a considerable increase in malignant thyroid tumors was also observed in adolescents : in 1991 : 20 cases, 1992 : 18 cases, 1993 : 18 cases and in 1994: 21 cases.

It should also be mentioned that between 1981-1985 the number of childhood thyroid cancers per 100.000 children population ranged 0.04-0.06 yearly. In 1990 this index increased up to 0.23, 1991 : 0.19, 1992 : 0.43, 1993 : 0.39 and 1994 : 0.36, thus 6.5-10 times exceeding the "pre-Chernobyl" level. As for several of the most contaminated regions of Ukraine this index was much higher. In 1993, it was 2.3 in the Kiev oblast, 1.5 in the Chernigov oblast, 1.3 in the Cherkasy oblast, 1.0 in the Zhitomir oblast and 0.7 in the Rovno oblast. There has also been marked increase of the incidence rate of 1.0 in the city of Kiev. In 1994 this index jumped to 1.6 in Zhitomir oblast and 3.8 in Chernigov oblast.

In absolute numbers in the period 1986-1994 there were 35 thyroid cancers registered in the Kiev oblast, 23 in the Chernigov oblast, 8 in the Rovno oblast, 13 in the Zhitomir oblast and 14 in the Cherkasy oblast. In the city of Kiev there were 27 cancers registered during this time. According to the preliminary data for 1995 the greater incidence was observed in Kiev oblast (8 cases), the city of Kiev (7) and Zhitomir oblast (4). It should be emphasized that in 1981-1985 period no cases of thyroid cancer were reported in the above-mentioned areas with the exception of the Cherkasy oblast. In general, the "contribution" of these highly contaminated regions to the incidence of thyroid cancer in children in Ukraine in the period of 1990-1994 makes more than 60%.

As for the age distribution of patients 0-18 years, operated during 1990-1994 it is obvious that in 1992-1994 there was an increase in patients under 10 years of age. This translates to these patients being under 6 years of age at the time of the Chernobyl accident. This age group was the most vulnerable to radioactive iodine exposure.

The female to male ratio has changed only slightly : 1.8:1 before the accident to 1.4:1 during the 1990-1994 period with a recent shift to males.

Therefore, a pronounced increase in thyroid cancer cases in children and adolescents in Ukraine have been obvious following the Chernobyl accident.

It is most probable that excessive cases of thyroid cancer in children in Ukraine are of radiation genesis since more than 60% of all cases were registered in the 5 most contaminated oblasts out of 25 oblasts of Ukraine.

Radiation thyroid doses in children and adolescents operated in 1994 for thyroid

carcinoma were estimated at the department of Dosimetry and Radiation Hygiene of the Scientific Centre of Radiation Medicine, Academy of Medical Sciences of Ukraine, under the guidance of Prof. I.A. Likhtarev.

As in the previous years in the majority of cases (79%) the absorbed thyroid dose did not exceed 30cGy, in 10.5% it was 30-100 cGy and in 10.5% - 100 cGy and more. The number of excessive cases of thyroid carcinoma as compared with the calculated spontaneous level per 100.000 children and adolescents was much higher in areas where thyroid radiation dose was 50-100 cGy and 100-200 cGy [2].

Analysis of the health state of patients aged 0-18 years with malignant thyroid tumors who were treated at the Department of Surgery of the Institute of Endocrinology and Metabolism in 1986-1994 showed that when admitted to the hospital, children had no complaints. Some patients complained of tumour-like formation in the neck, compression, hoarseness, problems with swallowing. In some children thyroid cancer was diagnosed when they were examined for submaxillary and cervical lymphadenitis.

Clinical thyroid cancer in children examined was characterised by cervical tumour-like formation of different size. Palpation showed solitary nodule, multiple nodules, diffuse tumour with vague contours. The size of palpable and ultrasonically identified nodules was 0.5-3.6 cm in diameter. In the majority of cases thyroid tumors were of extreme density, even stone-like, in this they differ from ordinary nodular goitre. The surface of the tumors, depending on the spread, was elastic, rugged or uneven.

One of differential diagnostic criteria of thyroid cancer is limited tumour nodule mobility. The degree to which this sign is manifested depends on the tumour size and its spread over the surrounding tissues. However, a soft nodule does not exclude thyroid cancer.

The treatment of thyroid cancers in children and adolescents in Ukraine is total thyroidectomy. Diagnostic scans with radioactive iodine-131 are performed 6 weeks after total thyroidectomy to reveal whether residual thyroid tissue or metastases are present. When areas accumulating radioagents are found they are ablated with therapeutic dose of radioiodine. The postoperative management of thyroid cancer also involves full-scale hormonal rehabilitation of patients.

A morphological study was carried out on 196 cases of thyroid cancer removed in 1986-1995 (by August 1st) at the Department of Surgery, Institute of Endocrinology, from children and adolescents aged 0-18 years. The male to female ratio was 1:1.3. In these cases the diagnosis of thyroid cancer was made by 4 pathologists in Kiev, according to the WHO classification [3]. 130 of these cases were additionally reviewed by the American expert in thyroid pathology Prof. V. LiVolsi in 1994 and 125 such cases were reviewed by the EU expert Prof. D. Williams (UK) and by Prof. B. Egloff (Switzerland). In 98.5% of cases the diagnoses were confirmed.

The results were the following:

- 183 cases of papillary carcinoma (93.4%)
- 6 cases of follicular carcinoma (3.1%)
- 4 cases of medullary carcinoma (2.0%)
- 2 cases of anaplastic carcinoma (1.0%)
- 1 case of malignant lymphoma (0.5%)

In patients who were operated in other Ukrainian clinics the diagnosis of thyroid carcinoma was verified by the local pathologist. Pathologic data for these cases will be

presented later after we and other experts confirm the analysis of these specimens. Thus, it is clear that following the Chernobyl accident papillary forms of carcinoma are most common in children and adolescents in Ukraine.

Histological analysis of papillary carcinoma revealed the following :

Prevalence of non-encapsulated tumors : 91.0%

Infiltration of adjacent soft tissue : 50.5%

Signs of intraglandular tumour spread when tumour sites are detected in relatively unchanged tissue : 55.3%

Typical papillary carcinoma was observed in 12.2% of cases. Papillary structures in the tumors studied were characterized by typical clear nuclei, usually oval or rounded. Nuclear chromatin was located mainly in the periphery and, as a rule, was absent in the central part, this gave the nucleus the "ground-glass" appearance. In addition, the papillary carcinoma cells were characterized by grooves, intranuclear inclusions and evidence of nuclear overlapping.

Electromicroscopically in papillary areas of carcinomas studied well differentiated thyrocytes were observed. They differed in the degree of functional activity. Cells with well developed cytoplasmic organelles prevailed showing granular endoplasmic reticulum, mitochondria, and the Golgi complex. The nuclei of the tumour cells were indented with low heterochromatin content and cytoplasmic "inclusions" into nucleoplasm, which is typical for this carcinoma pattern. These "inclusions" are not true intranuclear inclusions, but just reflect deep and complex nucleolemmal invaginations. Changes in the nucleus are very important diagnostic criteria of papillary carcinoma for cytologists and pathologists when studying the specimens with light microscope [4-5].

Follicular variant of papillary carcinoma was observed in 38.3% of cases. Nuclei in follicular areas are also clear and poor with chromatin. Typical papillary structures were not numerous or absent.

Solid or mainly solid variant was observed in 27.7%. Tumors with the alveolar-solid pattern prevailed, and tumour sites were divided by connective tissue.

Electromicroscopy revealed solid areas in the parenchyma consisting of poorly differentiated cells, when solid variants of papillary carcinoma were studied. Special attention was paid to details such as : smaller size, changed forms, presence of processes, and a decrease of organoid content [1-6]. Often only separate small canals of granulated endoplasmic reticulum, flocks or ribosomes, mitochondria and large vacuoles were observed, findings that are typical of the early stages of embryogenesis of endocrine glands. It should be pointed out that clusters of poorly differentiated cells were detected in the so-called uninvolved part of the thyroid gland thus indicating multifocal tumour growth.

Diffuse sclerotic variant of papillary carcinoma was observed in 3.7% and characterized by diffuse tumour growth, signs of sclerotic manifestations, lymphoid infiltration, prominent invasion of the tumour cells in the lymphatic vessels and a large number of psammoma bodies.

Mixed variant with papillary, follicular and solid areas was found in 18.1% of all cases.

It should be emphasized that irrespective of the variant of papillary carcinoma, solid clear-cell clusters in the areas of infiltrating tumour growth were found in 55.3% of cases. In addition psammoma bodies were present in 80.3% of cases, sclerotic stromal changes in 79.9%, and signs of background thyroiditis (9.6%) or lymphoid infiltration in 32.4% 67.6% of cases showed tumour invasion into lymphatic and 23.9% into blood

vessels.

Tumour vessels in children were characterized by oedematous endothelium protruding into the lumina and by reduced micropinocytotic activity on a background of thickened basement membranes. Such changes in the components of the vascular wall were described for radiation exposure [4].

From our point of view, ultrastructural criteria of the initial stages of metastatic spreading of tumour cells is most interesting. These tumour cells lose their intercellular bonds, become rounded and may be found both in the capsule of the gland and occasionally in the lumina of tumour vessels.

In lymph nodes, metastases were observed in 59.0% of cases. Metastases were characterised by typical papillary structures or follicular and solid areas. In the solid areas cell clusters had preformed nuclei similar in structure to the focus of origin.

In general, the described morphologic signs indicate comparatively rapid growth and highly invasive properties of these tumors, especially when patients' ages are taken into consideration. This aggressiveness is revealed by frequent distant metastases. At our institute 23.7% of cases in this age group showed metastases to the lungs at the time of surgery and at various periods after surgery.

A true comparison with pre-Chernobyl papillary carcinomas is difficult because in the period of 1981-1985 there were only 8 these tumors removed in the age group 0-18 years. Of these 75% showed a typical variant of papillary carcinoma, 12.5% a follicular variant and 12.5% a solid variant. Although both groups are not strictly comparable, there seems to be in the post-Chernobyl period, an increase in the solid and follicular variants of papillary carcinoma, the presence of diffuse sclerotic variant and evidence of highly invasive tumour properties (multifocal growth, capsular and vascular invasion, lymph node metastases and infiltration of the adjacent tissues).

It should also be mentioned that a great number of solid and follicular variants of papillary carcinoma on a background of aggressive tumour behaviour was registered in thyroid carcinomas in the children of Belarus [7,8].

The increase in the incidence of solid and follicular variants was noted in comparison to those described papillary thyroid carcinomas in children from Philadelphia [9], and United Kingdom [10].

The comparison of the thyroid cancers in Ukrainian children with the British series [11] shows that in the period of 1990-1994 175 children aged 0-14 years were operated in Ukraine (on average, 35 cases per year). During the 30-year period (1963-1992) 154 children were operated in the United Kingdom (on average, 5 cases per year), that is it was 7 times more common in Ukraine.

There were major differences in the age structure of the two series. In the United Kingdom there was a smooth increase with age after about 6 years, with a rapid increase after 10. This contrasts with the Ukrainian series, where the peak of incidence occurs at the age of 8, with a subsequent decline.

In British series the female/male ratio was 2.7:1, while in Ukraine it was 1.3:1, that is in this age group a shift to males was obvious in the Ukrainian series.

In the British series papillary carcinoma in children made only 69%, whereas in Ukrainian series they numbered 95% with a sex ratio of 3.8:1 (F:M) in the UK compared with 1.4:1 in the Ukrainian series. At that in the United Kingdom typical variant of papillary carcinoma was 2.4 times more frequent and on the contrary, the most unfavourable solid variant of papillary carcinoma was 2.3 times less common.

Thus, these observations have confirmed the occurrence of a very large number of cases of thyroid carcinoma in children in Ukraine since 1990, and have shown that the

Ukrainian tumors differ from thyroid cancer in children in the United Kingdom by being more common in younger children and in boys. Analysis of the subtypes of thyroid cancer shows that the increase is specifically in a solid/follicular type of thyroid carcinoma..

Molecular-genetic and immunomorphologic study of malignant tumors is one of the most promising topics of these times. Changes in numerous oncogenes, growth factors, tumour suppressor genes are observed in malignant tumors of different organs [12-14]. For poorly and well differentiated carcinomas various genetic pathways of carcinogenesis may exist [15,16]. Some of carcinomas may develop due to the accumulation of a number of genetic changes which, as a rule, closely correlate with tumour progression and metastasis.

There are many publications about the oncogene and growth factor expression in thyroid cancer [12-22]. These problems have not been investigated in the sphere of childhood thyroid cancers so far.

That is why with the Experimental Collaborative Project-8 (EC/CIS Collaboration project) in cooperation with Cambridge University together with Prof. D. Williams, Dr. G. Thomas and Dr. R. Harach, thyroglobulin, calcitonin contents were studied with the help of immunohistochemistry and in situ hybridisation. Besides, met, ret and p53 oncogene expression, in tumour cells, lymph node metastases and extratumoral microscopically unchanged thyroid tissue were studied using immunoperoxidase technique.

Immunocytochemistry showed uneven thyroglobulin distribution in tumour cells. In the solid areas and in the lymph node metastases thyroglobulin reaction was focal. The same was noted in thyroglobulin biosynthesis in solid areas, lessening of their differentiation [6], and it causes anxiety as far as the postoperative prognosis is concerned.

Calcitonin-containing cells were identified in tumour tissue only in 5% of cases while C-cell hyperplasia in the thyroid extratumoral tissue was revealed in 41% of cases thus proving a definite role of C-cells in oncogenesis of the thyroid gland. We had already paid attention to this phenomenon following our electromicroscopic investigations [1,6].

When studying oncogene expression the most pronounced reaction was shown for the oncogene ret, it was detected in 87% of cases and located both in papillary and follicular and solid structures. The most intensive reaction was observed in cells infiltrating the capsule or stroma of the tumour, these were mainly solid cell clusters. In positively stained cells reaction product was mostly seen near the basement membrane. Only in some cases there was positive staining in the luminal sites of tumour cells.

The oncogene met was detected in 74% of cases, mainly with diffuse cytoplasmic staining. Only in some sections membrane staining was obvious. The reaction was much less intensive than for the oncogene ret.

Data on identification of p53 gene also seem to be of interest. Its mutation in carcinoma and its visualisation indicate lessening of tumour differentiation. As far as we know this gene was detected in thyroid tumours only in anaplastic thyroid carcinoma [15,16]. In our study p53 gene was found in 56% of cases but in the majority of cases (65%) the number of immunopositive nuclei was very small, on average only 5-10%. But at the same time in 24% of cases the number of immunopositive nuclei was about 20% or more.

Thus, the data obtained once more confirm highly aggressive properties of the studied papillary carcinomas in children and indicate the necessity to continue the work

we have begun.

Further research in this field is necessary and could elucidate the mechanisms of carcinogenesis of the thyroid gland in children after the Chernobyl accident. A better understanding of the role of oncogenes in carcinogenesis of the thyroid gland may be helpful in determining specific tumour markers and be used for the earlier detection of these malignancies.

So we conclude that : After the Chernobyl accident in 1986, there has been an increase of thyroid cancer cases in children and adolescents in Ukraine. The incidence rate of thyroid cancer in these groups has increased most considerably since 1990.

These additional cases of thyroid cancer in children and adolescents, are most probably of radiation genesis, since more than 60% of all cases have been registered in the 5 oblasts most contaminated by the Chernobyl accident out of a total of 25 oblasts in Ukraine.

Thyroid cancers in children and adolescents in Ukraine have been mainly of the papillary carcinoma pattern. The aggressive biological behaviour is supported by frequent signs of multifocal growth, high invasive properties, intensive reaction to various oncogenes and growth factors. Such aggressive behaviour is also confirmed by regional and distal metastases.

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