Artykuł przeglądowy *Review*

Progerias and anticipative diseases

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Summary

Progerias or senescence syndromes are inherited diseases which develop during childhood and resemble an accelerated in time aging of a mature body. The few progeria types which have been described, i.e. Werner's syndrome, the syndrome of Hutchinson-Gilford, Cochainer's syndrome, Down's syndrome and ataxia teleangiectasia, reflect molecular defects in the repair of DNA. Recognition of etiopathogenesis and clinics of progeria would provide a chance for early detection of the diseases, e.g. in the prenatal period, as well as its more effective treatment. This, perhaps, may provide one of the keys for the recognition of the natural, extremely complex process of body senescence. Anticipative diseases, in turn, represent diseases of children which in their development outpace, even by a few years, and manifest a more acute course, than the same disease noted in the parents. The diseases result from unstable tandem trinucleotide repeats (TREDs). Diseases of this type include myotoic dystrophy 1 (DM1), Huntington's disease, syndrome of fragile X chromosome, Alzheimer's disease, Parkinson's disease, as well as most probably also chronic myeloproliferative diseases (CMDs), Turner's syndrome and Klinefelter's syndrome. An attempt was made to compare progerias and anticipative diseases but the problem is difficult to implement at the current condition of knowledge.

Keyword: progerias, anticipative diseases (anticipation)

Progerias or senescence syndromes represent inherited diseases which are manifested during childhood and resemble accelerated in time process of aging noted in the mature body (13). Their principal signs include retardation of growth, precocious wrinkles, atrophy of skin, subcutaneous tissue, and of muscles. Individuals with progeria manifest hyperlipidaemia with subsequent arteriosclerosis and catharact, disturbed metabolism of collagen, osteoporosis; they are also predisposed to develop malignant tumours. Progerias are accompanied by decreasing activity of genes coding for cyclins A, B, F and CDK1 (cyclin dependent kinase-1), which participate in the mitosis of a cell, as well as of genes responsible for duplication and repair of DNA, i.e. thymidilate synthase, PCNA (proliferating nuclear cell antigen) and helicase (12, 29). Genes are also present (around 30 of them in humans), which manifest an increased activity, e.g. genes controlling structure and function of extracellular matrix (ECM) with mediation of metalloproteinases, inhibitors of urokinase and certain proteoglycanes, which used to be quoted as an explanation of precocious senescence of skin and subcutaneous tissue (12).

In studies on the process of natural senescence it has been noted that newborn's fibroblasts divide *in vitro* around 65 times, fibroblasts of adult individuals around 50 times while fibroblasts of patients suffering from progeria only around 35 times (6). The dividing cells remain under effect of intracellular mechanisms, such as abbreviation of telomeres (tandem sequences of non-transcribed DNA, TTAGGG), progressive telomeres damage during senescence plays a causative role in activating progerin production. Among other types of intracellular mechanisms are effects of „clock genes", e.g. of *clk-1* gene in *Caenorhabditis elegans*, in which mutation of the gene elongates the life of a worm by 50%. Interestingly, sequencing of *C. elegans* genome demonstrated that 60-70% of genes in humans find their counterparts in the genome of the worm and provide a suitable experimental model in genetic comparisons between the taxons (24). Cells also manifest the ability of repairing damage of outer origin (25). However, the repair occasionally is incomplete and in such situations the experienced damage accumulates in the cell causing its senescence. The rate of cumulation of the errors is thought to be clearly directly related to the cell age. Among the principal causes of the phenomenon investigators mention free radicals (FR) and post-translational modification of intra- and extracellular proteins (26). It has been calculated that within one day as many as 100 thousand free radicals act on cellular DNA, mainly 0_2 -, H_2O_2, OH - (18).

FR act through oxidation of lipids in cell membranes, oxidation of proteins and damage of DNA, particularly of thymine and guanine, with formation of single strand breaks in the nucleic acid, exchange of chromatid fragments and formation of cross-links between DNA and protein (18, 22). In a reverse manner, the lower the amount of superoxide anionic radical in cell mitochondria, the longer is their survival, which may be attained, for instance, by diet with caloric restriction (20). Cells which have lost their ability to divide are responsible for a condition termed replicative senescence (12). In such cells the activity of beta-galactosidase appears, which cannot be noted in young cells. Although it was attempted to delay replicative senescence by inhibition of RB (*retinoblastoma*) protein or TP 53 protein (earlier termed p53) but after an additional 10-20 divisions the cells cease to divide anyway.

Progerias include a few pathological syndromes and the heritable ataxia, *ataxia teleangiectasia*. The syndromes include (12, 13, 30):

1 – Werner's syndrome or adult-onset progeria, characterised by mutated *wra* gene, which codes for rDNA helicase, resulting in other types of mutations, like the mutation of DNA deletion, the phenomenon of a rapid shortening of telomeres and defects of DNA replication. Such observations justify the statement that the syndrome represents a dynamic chromosomal mosaicism, which may result in an altered chromosomal structure, e.g., the presence of a ring chromosome (www.progeriaresearch.org). In such patients cells survive *in vitro* for much shorter periods of time than healthy cells, and their cell nuclei accumulate rDNA (4). In Werner's syndrome, loss-of-function mutations promote cellular senescence and neoplastic transformation.

2 – Hutchinson-Gilford Syndrome (HGPS) manifests all the suggestive traits of premature senescence, which appear at a very high rate (though most affected tissues are vascular smooth muscles): the affected patients die at an age of below 25 years (16). The progeria was described for the first time in 1886 by Jonathan Hutchinson and in 1904 by Hastings Gilford. At the age of 6-12 months affected children loose their hair, do not grow, their body weight decreases, their nose resembles an avian beak and their faces are disproportionally small for a given size of their head. Bones are thin, fragile, osteoporotic, the patients develop precocious arteriosclerosis, the skin is wrinkled, yellow and looses elasticity (2, 3, 8). Relevant to the pathogenic mechanisms of HGPS might be oxidative stress. Until now, only 150 cases of the disease have been described all over the world. It is known that over 400 distinct point mutations have been identified so far throughout the LMNA gene, which result in the development of at least ten distinct human disorders, collectively known as laminopathies, among which is the premature aging disease HGPS. The Hutchinson-Gilford syndrome is most commonly induced by substitution of cytosine by thymidine in the *LMNA* gene, coding for laminins A, C and a mutant of lamin A, namely E145K-lamin A (in mammals other than humans also for laminins B1 and B2), i.e. for proteins (progerins), lining inner aspect of nuclear envelope which belong to intermediate filaments of V type, controlling gene expression, as well as distribution and stability of other proteins (27, 28). The majority of HGPS cases are associated with a point mutation which is located in the codon 608 within 11th exon of *LMNA* gene, resulting in an abnormal splicing and production of prolamin A, lacking 50 amino acid residues at C-terminus of the polypeptide chain (9, 31). The prelamin looses the position which allows for its proteolytic splicing and its transformation to laminin and for the accumulation of farnesylated prolamin A, with subsequent evident deformation of nuclear envelope, increased frequency of DNA damage and modification of hitone proteins (18). Recent studies have suggested that the accumulation of farnesylated prelamin intermediates may play a role in the aging processes. A similar injury of DNA and modification of histones was observed in fibroblasts of elderly (80-96-year-old) individuals. The lesions arose due to the mobilization of a hidden site for mRNA cumulation of the *LMNA* gene, leading to formation of an abbreviated form of lamin A (6). Parallely, the blocking of the site allows for a reversibility of the senescence-associated lesions. Independently of the observations, mice with a knockout of *zmpste 24* gene and treated with an inhibitor of farnesylotransferaze ABT – 100 in *in vitro* studies manifested a reduced deformation of cell nuclei, previously affected by the progerin deposit (7, 33).

Recently, the presence of a mutation was demonstrated within the *XPF* gene, which codes for a portion of the enzyme responsible for repair of DNA damage. The mutation is linked to an absence of protein with properties of DN-aze. The other portion of the enzyme is coded by the *ERCC1* gene, allowing for the binding of a protein with the damaged fragments of a DNA strand (1). Thus, mutations in *XPF* or *ERCC1* genes decrease activity of the principal repairing enzyme. The observations were corroborated on mice lacking the genes, which, e.g., had problems with production of somatotropin and insulin, manifested an increased cell mortality and a disturbed DNA repair, while in external inspection resembled old animals.

3 – Cochayner's syndrome reflects a mutation in *cs beta* gene, coding for ATPase family, SWI2. Signs of senescence rapidly appear, with hypersensitivity to light, damage to the central nervous system and hypogenitalism and death develops up to the 40th year of age. Cells of the patients manifest an impoverished transcription of DNA-repairing proteins (12).

4 – Down's syndrome involves trisomy of chromosome 21, in which around 95% patients carry the total chromosome number of 47, and the chromosomal non-

disjunction occurred in meiosis. The additional chromosome almost always (95%) originates from the mother (13). Despite the knowledge that chromosome 21 contains 225 genes, the molecular basis of Down's syndrome is not known in detail. The disease is manifested by inborn errors of the heart, a propensity to infections, mental retardation and an increased incidence of megakaryocyte leukaemia. In such patients Alzheimer's disease becomes manifested much earlier, providing as if an example of an anticipative disease (12). Apart from Down's syndrome, other, less frequently encountered, trisomies include Edward's syndrome (trisomy 18) and Patau's syndrome (trisomy 19) of a very severe clinical course and morphological defects, leading to death of the affected child already in the first year of life. The syndromes reflect sequels of non-disjunction during meiosis of an oocyte or a balanced translocation in one of the parents (13).

Ataxia teleangiectasia develops due to a mutation of the *atm* gene, coding for the protein kinase of phosphatidylinositol (serine-threonine kinase of ATM, a very sensitive indicator of DNA damage) and located on chromosome 11q22 – 23. The defect is followed by a delayed phosphorylation of TP53 protein (earlier termed p53), and, subsequently, its cumulation, shortening of telomeres and defects in DNA repair, abbreviation of replication time of the nucleic acid, as well as disturbances in the process of apoptosis (25). When both alleles of *atm* are mutated, the cell cycle continues and the cells divide transmitting the damaged DNA further on, which was empirically demonstrated in studies on the action of ionizing radiationon healthy skin. The disease is inherited in the autosomal recessive manner with a frequency of 1 case per 300 thousand deliveries. Apart from dilations of peripheral blood vessels, morphological defects involve mainly the central nervous system (atrophy of Purkynje cells and sometimes the presence of Ley's bodies), immune system (decreased levels of IgE and IgA) increased incidence of leukaemia and lymphoma and an accelerated process of senescence. The patients live short as a rule dying before the 20th year of age (29).

Recently, in the pathomechanism of progeria in animals particular attention has been drawn to the activity of cellular autophages. In eukaryotic organisms, during evolution autophages acquired the ability to maintain homeostasis in the body by protein degradation. Thus, Marino et al. (15) noticed that the activity of autophages in mice decreases with cell senescence, which probably reflects their damage and accumulation of errors, as well as, reciprocally, the high activity of autophages leads to a longer life. With such a mechanism one deals in progeria, in which the activation of autophages takes place in place of the typical decrease in their activity. Moreover, this unexpected increase in activity is linked to an entire series of metabolic alterations resembling those encountered upon a restricted caloric supply in animals or starvation. In turn, Nam et al. (17) examined discopathy in the mouse model of human progeria syndrome, induced by a deficiency of ERCC1 – XPF endonuclease, i.e. the enzyme involved in DNA repair. An evident shortening of the discs was demonstrated and degenerative lesions within the discs, involving a decreased content of proteoglycans as a result of DNA damage and an intensified apoptosis or changes typical for senescent mice. A similar morphological pattern can be obtained in mice without the above mentioned enzyme following experimental administration of mechloretamine. The conclusion follows that discopathy involving the degeneration of intervertebral discs represents a very complex process and depends on age, genetic predisposition, mechanical trauma and certain environmental factors, e.g. tobacco smoking.

The manifestation of progeria in humans provided a stimulus for intense genetic studies on the diseases in experimental animals. An interesting role in progeria may be played in mice by the *klotho* gene (10), the expression of which was detected in gastric glandular cells, neurons of muscular membranes, smooth muscle cells and interstitial ICC cells (Cayal's cells) using various methods, i.e. IF examination, confocal microscopy, flow cytometry and PCR. In mice without the *klotho* gene the number of ICC and ICC stem cells was noted to be decreased while the number of neurons remained unchanged, which was accompanied by a permanent synthesis of nitric acid in neurons and of miosin in smooth muscle cells. The amplitude of gastric contractions was reduced but the duration of emptying of the stomach remained unaltered. Mice without such a gene were cachectic, they produced less insulin, insulin-like growth factor (IGF-1) and growth factor of stem cells. Deficiency of the gene accentuated also oxidative stress of ICC cells. Overall, the conclusion was drawn that the mice manifested a significant similarity of morphological lesions within the stomach to lesions observed in humans suffering from progeria (10).

A detailed recognition of etiopathogenesis and clinical aspects of progeria would provide a chance not only for early detection of the diseases, for instance in the prenatal period, but also for their effective treatment. It might also provide clues to the recognition of the natural, extremely complex process of body senescence.

The cause of progeria and *ataxia teleangiectatica* involves defects in DNA repair and, reciprocally, less extensive DNA damage and more efficient repair of DNA may prevent development of the diseases. This indicates serious clinical implications since, apart from inducing a markedly accelerated senescence, progerias increase incidence of tumours.

Anticipative diseases

Anticipative diseases, or outpacing diseases, represent diseases which might be forecasted. Over the

course of generations develop earlier, even by 12 years, and manifest a more acute course than in parents of the patient, e.g. in glaucoma. They represent consequences of unstable microsatellite sequences and, thus, they have a molecular background. Anticipative diseases are inherited in a dominant manner and become increasingly intense in consecutive generations, developing at an increasingly early age of the patients. They result from unstable tandem repeats of trinucleotides (TREDs: triplet repeat expansion diseases). It was noted also that clinically healthy parents may carry tandem repeat numbers close to the upper limit in the norm, which may indicate that the mutation involves gene amplification (13). In general, anticipative diseases result from unstable sequences composed of the mentioned above repeats of trinucleotides (fig. 1). The exmples include:

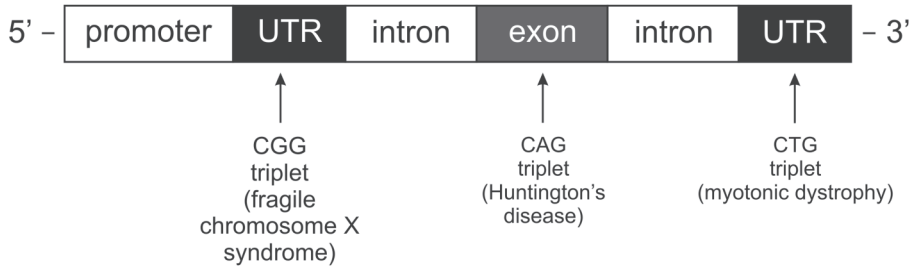

Fig. 1. Selected diseases which reflect mutations involving repeats of nucleotide sequences. Sites of expansion of pathological sequences. UTR = untranslated region; C = cytosine; A = adenine; G = guanine;T = thymine. Modified, according to Maitre and Kumar (13)

1 – Myotonic dystrophy (DM1), inherited in an autosomal dominant manner and appearing in humans with the frequency of 1 case per 8,000 deliveries. It is transmitted exclusively by the mother. The disease appears at pubescence and becomes manifested by a progressive weakening of muscles, particularly at the phase of relaxation (the so called effect of a closed fist), cataract, cardiomyopathy, frontal hair loss in males and a reduced intelligence. The gene responsible for the disease is located on chromosome 19q13.2.–13.3 and it codes for cAMP-dependent protein kinase (myotonin). Mutation of the gene leads to an unstable sequence of tandem repeats of CTG trinucleotide (13). The process takes place during oogenesis. The multiplication of CTG triplets takes place in the gene fragment which does not undergo transcription or translation. The length of CTG tandem repeats increases in consecutive generations, intensifying clinical signs/symptoms as an exponent of an increasing length of gene expression (12).

In morphological patterns neurofibrillar plexuses are observed, which in their outlook resemble plexuses noted in brains of patients with Alzheimer's disease. Muscular fibres undergo necrosis and become subsequently substituted by adipose or fibrillar connective tissue, while in the still persisting fibres increased numbers are noted on centrally arranged cell nuclei.

2 – Huntington's disease (*chorea Huntingtoni*) is inherited in an autosomal dominant manner with incidence of 1/20,000 persons. It appears at a moderate age (30-40 years) and, thus, with a significant delay and becomes manifested by a degeneration of cerebral nervous substance, dementia and chorea. The cause of the disease involves the elongation of a chain of tandem repeats of trinucleotide CAG pair, since the responsible gene, located on chromosome 4 (4p16.3) contains around 70-100 repeats, instead of 9-34 as in healthy persons, with an increasingly early manifestation of the disease reflecting a higher number of repetitions (32). The normal Huntington undergoes a mutation which disturbs the functioning of the protein on the unaltered allele. This represents an example of the gain of function mutation. The process takes place during spermatogenesis and, thus, the disease is transmitted exclusively by males. Morphologically, the disease is manifested by an atrophy of nucleus caudatus and cerebral putamen, with accumulation in cell nuclei of neurons and/or in their projections of Huntington protein in the form of inclusions, produced by the wild type gene and the mutated gene. The role of the protein remains unknown, although it is hypothesized that it may provide a substrate for caspase 3 enzyme, participating in apoptosis of cerebral neurons. Transmission of the gene through consecutive generations leads to an increasing length of repeats of the sequence and an increasingly early age of the development of the disease. Huntington's disease represents as if a converse of Parkinson's disease, since in the former a prevalence is noted of a dopaminergic system over cholinergic system and GABA-ergic system in cerebral striatum. Degeneration of inhibitory GABA-ergic neurons in the patients results in hyperinesis, dystonic movements or movements characterized by abrupt contractions (13).

It should also be stressed that Huntington's disease appearing, as mentioned above, at a moderate age is frequently manifested by anticipation or manifestation of clinical signs/symptoms at an increasingly young age in consecutive generations. The signs/symptoms manifest certain variability depending on genes passed by the mother or father (gene imprinting).

3 – Syndrome of fragile chromosome X, reflecting mutation of the *FMR1* (familial mental retardation 1) gene in the region 5' undergoing no translocation and manifested exclusively in males by mental retardation and macrogonadism (6, 11). *FMR1* gene is located on the chromosome Xq27.3 (the so called fragile region: the chromosome looks as if it was fractured). The number of CGG motive repeats in the *FMR1* gene amounts to approximately 29 in healthy individuals and to 52 to 230 in the patients. The effect involves a suppression of FRM protein synthesis, with particularly vast representation in the brain and male gonads. FMRP

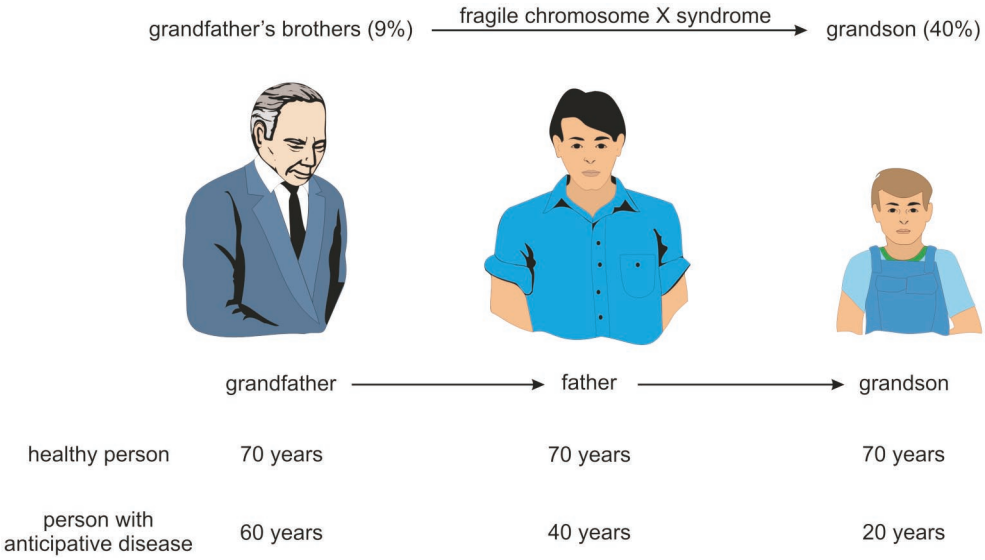

Fig. 2. Scheme of anticipative (outpacing) disease

protein manifests the ability to bind other proteins and RNA, while in neurons it reaches up to post-synaptic termini of dendrites as a portion of the ribonuclein complex (19). Simultaneously, it has been noted that around 20% of men with the mutated *FMR1* gene manifest no pathological signs/symptoms but, nevertheless, they remain carriers of the mutation, which is inherited by their grandsons with the mediation of their phenotypically normal daughters. And, therefore, brothers of a carrier suffer from the disease in only 9% of the cases while his grandsons suffer in as many as 40% of the cases, which is termed the paradox of Sherman (13) – fig. 2.

Among other diseases in the group myelo-bulbar neuropathy should be distinguished, linked to chromosome X, and myelo-cerebellar ataxias, described in detail in specialized treatises. The anticipation also accompanies some neurodegenerative diseases, developing at a decisively later age, e.g. Parkinson's disease or Alzheimer's disease (chA). The amyloid, which accumulates in chA, originates from the Alzheimer precursor protein (APP); the protein which is contained in the amyloid involves APP fragment, or Abeta protein or A4 protein. The respective molecular disturbances depend on genes on chromosomes 21, 19, 1 and 14 (5). The gene present on chromosome 14 codes for presenilin 1, and the gene on chromosome 1 codes for presenilin 2 (5). Mutation of the genes leads to increased amounts of Abeta protein, which rapidly turns into amyloid, providing senile plaques. Thus, within Alzheimer's disease two groups of patients can be distinguished: group I of an early beginning, inherited in a dominant autosomal manner, and group II, appearing at an older age, in which the manner of inheritance has not been fully clarified yet, although inheritance of a single allele of apolipoprotein epsilon (apo epsilon-4) is followed by a many-fold higher (2-8 ×) risk of the disease. In morphological patterns the presence of senile plaques and intraneuronal neurofibrillar plexuses are seen in the central nervous system, consisting of tau protein, which binds cellular microtubules. Moreover, neurofibrillarplexuses are formed by MAP-2 (myelin associated protein), ubiquitin and beta-amyloid. In turn, genetic factors responsible for Parkinson's disease remain unknown, although for a time it was assumed that a mutation might have occurred in the gene coding for a normal protein of nerve synapses, alpha-synuclin (14). Taking of methylophenyltetrahydropirine (MPTP) by narcomans induces a severe Parkinsonism in young individuals, which is supposed to point to an exogenous cause of the disease (13). Similar observations were recorded in experimental animals administered with MPTP together with monoaminooxidase, which manifested toxicity of the compound while inhibitors of MPTP inhibited development of the disease. Parkinson's disease is accompanied by decreasing concentrations of dopamine DA), enzymes of its synthesis, i.e. tyrosine hydroxylase (TH) and DOPA decarboxylase, which also decreases the amount of gammaaminobutyric acid (GABA), its decarboxylase, somatostatin and of some other neuropeptides. Due to reciprocal compensation, pathological signs cannot be noted until death of around 80% of the cells in the cerebral nigrostriatal system. The observed lesions include atrophy of dopaminergic neurons in substantia nigra and locus coeruleus and presence in the cells of hyaline inclusions in the form of Levy's bodies, composed of the earlier mentioned pre-synaptic protein, alpha-synculin. Thus, in the background of certain diseases (Alzheimer's disease, Parkinson's disease, Huntington's disease) an aggregation of abnormally coiled proteins can be detected, which takes place in the ubiquitine system of proteasomes with the participation of cellular chaperones (5).

Recently, attempts are being made to also include among the anticipative diseases chronic myeloproliferative disorders (CMD), representing clonal proliferative lesions of the haemopoetic system, in which in 70% of the cases chromosomal disturbances can be detected, involving loss of the entire chromosomes or a deletion of long arms of chromosomes 5 (del 5) or 7 (del 7) (12). It is also assumed that the mutation of the *JAK2 (V617F)* gene is responsible for CMDs (Rumi et al. 2007). In CMDs bone marrow is rich in megaloblasts, micromegakaryocytes or atypical blasts, and the disease used to affect older men (50-70 years of age), in whom in addition an acute myeloblastic leukaemia (AML) may develop (9).

Most of neoplastic diseases of the CMD type undergo under a single form, i.e., either as chronic myelogenous leukaemia (CML), true polycythaemia, myeloid metaplasia, myelofibrosis or true thrombocythaemia. In the cases of CML a reciprocal translocation appears of the long arm of the chromosome 22 (Philadelphia chromosome, Ph) with the long arm of chromosome 9 (9). The translocation responsible for the development of the Ph chromosome creates the fusion gene of *BCR-ABL*, which plays a principal role in the neoplastic transformation. The chimeric gene codes for a protein consisting of a portion of BCR and the ABL tyrosine kinase domain. The appearing fusion protein is manifested by an increased activity of tyrosine kinase, which is decisive for development of CML. The proliferating elements include mainly the granulocyte line; therefore adult granulocytes fill bone marrow and peripheral blood. On the other hand, in the remaining described below myeloproliferative syndromes no genetic anomaly in the form of Ph a chromosome is observed. In the true polycythaemia all elements of bone marrow stem cell are observed to proliferate, including erythrocytes, granulocytes and megakaryocytes. Viscosity and density of blood increase, the potential for development of DIC (disseminated intravascular coagulation) syndrome increases, together with the potential for classic thrombi and infarctions. A disturbed function of blood platelets promotes hemorrhages. With progressing time, the bone marrow becomes fibrotic and its haemopetic role is taken by the spleen, which undergoes a marked proliferation. Following bone marrow metaplasia and, subsequently, fibrosis haematopoetic activity takes place mainly in the spleen, liver and lymph nodes; however, this is abnormal and of low efficiency, which may result in severe anemia and thrombocytopoenia. In the bone marrow neoplastic megakaryocytes arise, which produce factors stimulating the proliferation of the fibroblasts: PDGF (plateled-derived growth factor) and TGF (transforming growth factor beta), which, acting as mitogens on fibroblasts, induce progressive fibrosis of the bone marrow. Comparative studies on familial CMDs and the sporadic form of CMDs in 458 patients demonstrated no significant differences between the groups, but in either form the diseases were noted to appear earlier in the second generation, which was accompanied by the shortening of telomeres in progeny as compared to the generation of the parents (21). The two traits are supposed to provide evidence permitting to include CMDs to anticipative diseases.

Most probably, anticipative diseases also include Turner's syndrome (monosomy 45,X0 or mosaic forms, 45X0/46XX, 45X0/46XY, with partial deletion of chromosome X), in which women who carry just one chromosome X in every somatic cell suffer from disturbances in the gonads, that are manifested by an accelerated loss of ovarian oocytes to the extent that their apoptosis becomes completed already in the second year of life and the gonads form just a thin streak of connective tissue devoid of oocytes (12). Such a pattern of morphological lesions justifies the notion that a premenopausal period in the females „overtakes" the period of pubescence. Moreover, the disease is manifested by the low concentration of serum estrogens and high levels of gonadotropins, as well as , in 70% of the cases, by the absence of sex chromatin. The other numerous clinical signs include low stature (lack of a single copy of *SHOX* gene, situated on chromosomes X and Y), defects of heart and kidneys, diabetes mellitus type II, autoimmune thyroid struma, and a tendency to develop gonadoblastoma tumor (20). The group of diseases may also include Klinefelter's syndrome which, similarly to Turner's syndrome, is a disease of cytogenetic background, dependent on sex chromosomes: the syndromes result from non-disjunction of sex chromosomes or they result from numerical chromosomal aberrations. In women this may lead to the formation of a single cell with two chromosomes X (XX) and one devoid of a sex chromosome (–), and in males in the formation of a single cell with two chromosomes, X and Y, and a single cell with no sex chromosomes (–). Klinefelter's syndrome develops in males with the incidence of 1 affected man per 1000 men and it is linked to the karyotype of 47,XXY or a mosaicism 46,XY/47,XXY. In newborns, dysgenesis of seminiferous tubuli develops, which becomes intensified with progressing age, rapidly leading to hyalinization and their fibrosis as well as to partial proliferation of Leydig cells and hypogonadism (23).

As a rule, genetically conditioned diseases are manifested already at delivery, but there exist diseases such as Huntington's disease which do not become manifested until a mature age. Their frequent cause involves mutations or stable alterations in DNA, transferred by sex cells to progeny, while mutations of somatic cells are not inherited but they frequently represent the cause of tumors. A specific form of the mutations involves trinucleotide repeat mutations, i.e. amplification of trinucleotide sequence always involving guanine (G) and cytosine (C), as well as the fact that the extent of amplification increases during gametogenesis. A classical example of the phenomena is provided by the syndrome of fragile X chromosome. The diseases represent a group of heterogeneous, genetically conditioned disturbances which do not follow the classical principles of inheritance according to Mendelial rules (12).

Summing up, it should be stressed that anticipative diseases are not equivalent to progeria. Nevertheless, development of a disease earlier than that dictated by gene inheritance may clearly accelerate body senescence and even death of the body. In either case genetic similarity can be traced between cells despite the difference in time (despite the elapsing time) which

is clearly abbreviated both in progeria and in anticipative diseases. Nevertheless, the similarity at the moment is difficult to be fully proven (fig. 3).

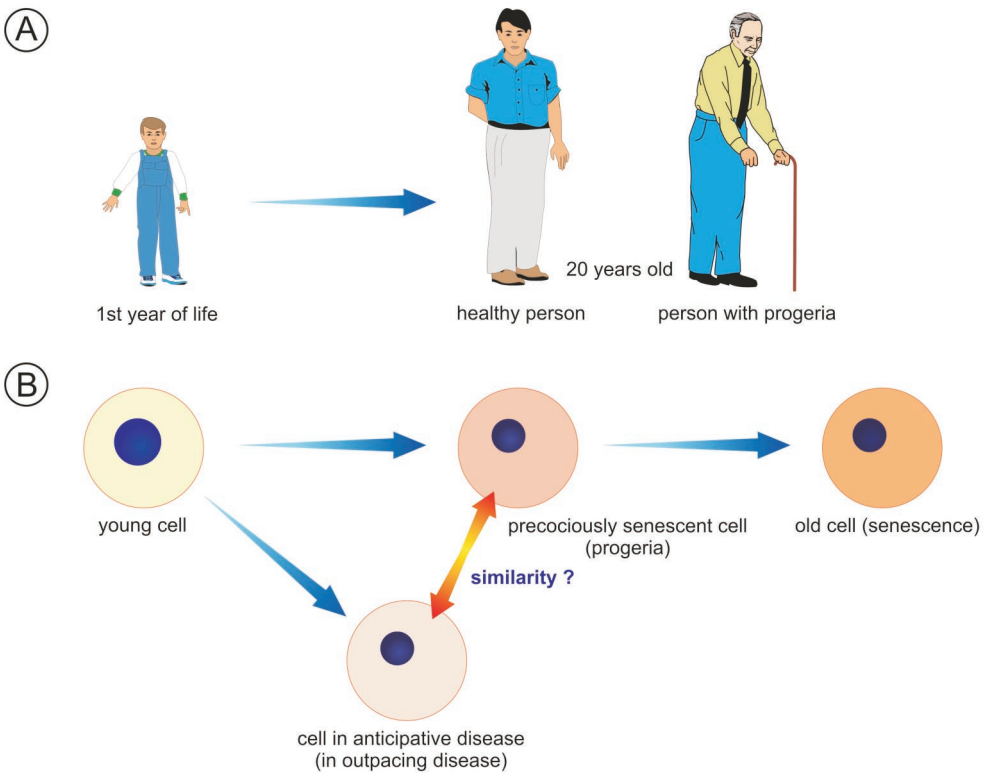

Fig.3. Scheme of progeria and its hypothetical similarity to anticipative diseases

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