Neurodegenerative disease in infants with multiple congenital malformations — report of two cases

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During embryogenesis, about 40% of genes are involved in the development of the central nervous system (CNS). The same genes support the integrity and function of brain cells in humans. Birth defects cause different changes in genetic material during embryogenesis. They may also be responsible for precocious death of cells in postnatal period. We studied cases of two infants with similar congenital defects (prenatal onset growth deficiency, coloboma of iris, epicanthal folds, low set ears, clinodactyly of Vth fingers). The infants died at age 9 and 10 months with signs and symptoms of progressive CNS degeneration. In one case, chromosomal aberration was detected (4pter). Neuropathologically, there were small for the age brains, atrophy of cerebral cortex, white matter and basal ganglia (mainly nucleus caudatus) with loss of neurones, spongiosis and hypertrophic astroglia reaction as well as atrophy of cerebellar cortex. Severe damage of white matter was seen. We suggest that such cases are natural models for investigations of the role of genes in embryogenesis and pathogenesis of neurodegenerative diseases.

key words: neurodegenerative disease, congenital malformations, chromosomal aberration, 4pter, prenatal onset growth deficiency

INTRODUCTION
It is estimated that about 40% of genes are involved in the development of the central nervous system (CNS) during embryogenesis. These genes regulate proliferation, migration, differentiation and maturation of cells. The same genes support the integrity and function of brain cells in humans [7, 8]. Birth defects cause different changes in genetic material during embryogenesis. They may also be responsible for precocious death of cells [7, 8].

We studied cases of two infants with multiple congenital defects, which died with signs and symptoms of progressive neurodegeneration disease. Chromosomal aberration was only detected (4pter) in one case, but clinical and neuropathological pictures in both cases were similar.

MATERIAL AND METHODS
We analysed clinical data of two infant cases with multiple congenital malformations and progressive neuronal disease. The brains were fixed in formalin. Then, specimens from cerebral hemisphers, brain stem and cerebellum were taken and embedded in paraffin. The sections were stained with hematoxylin-eosin (HE), Kluver-Barerra and Bielschovsky methods; GFAP reaction was made on some slices.

CASES REPORT
Case I
A girl was born after uneventful full term pregnancy and delivery with signs of intrauterine dystrophy (birth weight 1800 g, length 42 cm, and head circumference 29 cm) with low Apgar score. Multiple congenital malformations were diagnosed (Table 1). USG of the brain...
was described as normal. From the day of birth, she failed to thrive and showed no signs of psychomotor development. There was chromosomal abnormality detected (addition of short arm of 4th of chromosome). Difficulties in controlling seizures started at the age of four months. At the age of five months, she was microcephalic, developmentally delayed, spastic, with no signs of swallow and sucking. Brain CT showed dilatation of the whole ventricular system and periventricular focal leukomalacia. EEG showed generalised epileptic changes. She died at the age of 9 months. Clinical diagnosis showed multiple congenital malformations and damage of the central nervous system in the child with chromosomal aberration.

Case II
A girl was born after uneventful pregnancy after 41 weeks of gestation with signs of intrauterine dystrophy (birth weight 1350 g) with low Apgar score. She was dysmorphic with multiple congenital malformations (Table 1). At the age of five months, she was microcephalic, failed to thrive, developmentally retarded, and spastic. She could not produce any reaction to stimuli except poor cry. Periodically, there were ventilation problems and tonic fits. The karyotype was assessed as normal — 46, XX (routine GTG stain). USG picture of the brain at the age of 3 months was normal. She died at the age of 10 months. She was clinically diagnosed with multiple congenital malformations and damage of the central nervous system.

Table 1. Congenital anomalies

<table>
<thead>
<tr>
<th>Congenital anomalies</th>
<th>Case 1</th>
<th>Case 2</th>
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<tbody>
<tr>
<td>Microsomia (prenatal onset</td>
<td>+</td>
<td>+</td>
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<tr>
<td>growth retardation)</td>
<td></td>
<td></td>
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<tr>
<td>Bilateral iris defect</td>
<td>+</td>
<td>+</td>
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<td>Epicanthal folds</td>
<td>+</td>
<td>+</td>
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<td>Hypertelorism</td>
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<td>Low set ears</td>
<td>+</td>
<td>+</td>
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<td>Cleft of lip and palate</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Heart defect</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Microstomia, micrognatia</td>
<td>-</td>
<td>+</td>
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<tr>
<td>Additional costs</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Spina bifida occulta</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Duplication of right kidney</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Trachea, lungs and diaphragma dysplasia</td>
<td>-</td>
<td>+</td>
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<tr>
<td>Clinodactyly of Vth fingers</td>
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GENERAL AUTOPSY IN BOTH CASES CONFIRMED THE CLINICAL DIAGNOSIS

Neuropathology
Case I
Macroscopically, the brain (297g) appeared small for the age. It had signs of general atrophy with very narrow nucleus caudate and discoloration of the gray matter (Fig. 1A). There were small cavities in the white matter, basal ganglia and in some places of the cortex. There was also cerebellar atrophy (Fig. 1B). Microscopically, two kinds of brain malformation were seen: undivided focal brain gyri and subpial glio-neural heterotopies. There was diffuse cortical damage, with fine spongiosis in superficial layers, neuronal loss and hypertrophic astrocytic gliosis (Fig. 2). In caudate nucleus and focally in other basal ganglia, neurones and neuropil were replaced by hypertrophic astrocytes (Fig. 3). Small cavities and glial scars were visible in the cerebral cortex and basal ganglia. The myelination of the brain hemisphere white mater (Fig. 4A) was poor for the age of the brain. The brainstem cortico-
spinal tracts were hypoplastic (Fig. 4B). The white matter was severely damaged with astroglia reaction (Fig. 4C). The cerebellar cortex was atrophic with gliosis (Fig. 5).

Case II

Macroscopically, the brain (340 g) appeared small for the age. It had severe atrophy with very flat narrow
caudate nucleus (Fig. 6) and marked cerebellar atrophy. The damage of the diffuse grey matter was observed microscopically. There was neuronal loss, hypertrophic astrocyte gliosis and spongiosis in the superficial and deep cortico-subcortical layers. In the cortex, there was also focal necrosis with macrophages reaction. The neurones and neuropil were replaced by hypertrophic astrocytes — focally in the cortex (Fig. 7) and totally in the caudate nucleus (Fig. 8). There was diffuse cerebellar atrophy. Myelination was adequate for the age, but cerebral and cerebellar white matter was narrow with scanty myelin in axis of cerebral gyri (Fig. 9).
DISCUSSION

In the reported cases, the clinical course and multiple congenital malformations were similar. In both cases early disturbances of the brain development were clinically manifested by small head circumference for the age and lack of early psychomotor development. Hypoplasia of cortico-spinal tracts indicated early foetal damage of brain structures. During their lifetime, both infants developed neurological signs and symptoms of neurodegenerative disease, which later caused their deaths at similar age. The chromosomal aberration (addiction –4p+) was only found in the first case. In the second case, only routine chromosome stain technique was performed many years ago. It is possible that submicroscopical or molecular rearrangements might have been overlooked. Distal part of the short arm of chromosome 4 is rich in genes. It is the region in which the putative Huntington disease IT15 gene, FGFR3 gene,
which is mutated in skeletal dysplasias, as well as genes involved in Wolf-Hirschhorn syndrome are located [5].

In Wolf-Hirschorn syndrome (WHS), which is often caused by microdeletion of distal part of chromosome 4, there are prenatal onset of growth deficiency, microsomy, profound mental deficiency, cleft lip and palate, coloboma of iris and retina, facial dysmorhism, sometimes anomalies of heart, urine tract and others [1, 2, 4]. Tendency to intractable seizures has also been observed. About 20% of patients die in infancy. Many signs of WHS were present in both cases we have presented. However, the WHS is caused by deletion of genetic material, but it is well known that in mammals both deficits as well as addition of genes are deleterious (pathogenic). In both cases, we also noticed prominent brain cortex and caudate nucleus atrophy — similar changes as in Huntington disease [3, 6]. We presume that genes putative for WHS as well as others located in the 4pter might have been involved in the presented cases. We also suggest that such cases are natural models for investigations of the role of genes in embryogenesis and pathogenesis of neurodegenerative diseases.

REFERENCES