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Rubinstein—Taybi syndrome in pediatric neurology

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In this article present the basic information about a rare congenital multisystem genetic pathology-Rubintein—Taybi syndrome. The mandatory component of syndrome is a severe lesion of the central nervous system and the progressive character of mental retardation. It was considered the modern clinical, diagnostic, neurological and genetic aspects of this syndrome. There were described clinical case of the patient with this pathology during examination and treatment in the department of children's psychoneurology of the Institute of Pediatrics, Obstetrics and Gynecology National academy of medical sciences of Ukraine.
Keywords: Rubinstein—Teybi syndrome, clinic, diagnostics, prenatal diagnostics.

Congenital and hereditary pathology, especially associated with disturbances of central nervous system (CNS), organs, and systems of organs has significant effect on mortality and disability in children. According to World health Organization (WHO) data, 20 % of children morbidity and disability, as well as 15–20 % of children mortality are caused by congenital abnormalities. Effect of environmental harmful factors causes 10% of birth defects, 10 % are caused by chromosomal changes, and other 80 % have mixed character. Each year 50 % of children are born with congenital defects, at that one half of abnormalities is severe and demands appropriate surgical intervention, while congenital CNS abnormalities constitute 25 % of all birth defects [2, 3, 6]. Considering that in many cases congenital abnormalities appear sporadically — the most effective method for their prevention is timely and complex prenatal diagnostics and differentiated diagnostics aiming at decrease in children disability and creation of effective system of prognostics and treatment-prevention help.

Rubinstein—Taybi syndrome (syndrome of wide 1st finger of hands and feet, specific face look and mental retardation) is rare multisystem genetic pathology, which is characterized by progressing mental retardation, growth and bone age retardation, wide terminal finger bones and toe bones, characteristic cranial and facial features (beaklike nose, hypertelorism, heterotropy, high gothic palate, antimongoloid slants, ptosis), accompanied by microcephaly [13, 36, 47]. This disease is inherited by autosomal dominant type and is associated with deletions in 16th chromosome short shoulder (16p13.3). At present, the majority of registered cases appear sporadically due to de novo mutation in locus 16p13.3; however, there are reports about the syndrome manifestation in monozygotic twins and family cases. As this syndrome causative factors mutations in genes were identified — CREBBP and EP300, with functional disturbance of binding multidomain protein CREB, which is transcription co-activator and plays important role in cells growth and division regulation and foetus normal development. In case of this protein concentration decrease the normal development is disturbed before and after birth, and signs of Rubinstein—Taybi syndrome are formed [20, 29, 33, 42, 49]. This pathology symptom complex was at first described in 1957 by J. Michail and co-authors [30]. In 1963 paediatrician J.G.Rubinstein and roentgenologist H.Taybi singled it out as individual syndrome [37], which takes place in 1 case for 100 000 — 125 000 newborns [21]. Boys and girls are affected with similar frequency. If the pair has already had a child with this syndrome, possibility of another child birth with such disturbance is about 0.1 % (empirical risk for siblings). Patient with Rubinstein—Taybi syndrome has 50 % risk to give birth to a child with this syndrome [22]. In 39% of cases during pregnancy hydramnion takes place. After birth up to 20 % of newborns should be treated in intensive care department due to breathing disturbances, swallowing disturbances and apnoea episodes [23].

It should be noted that diagnosis of Rubinstein—Taybi syndrome is usually established after birth, generally on the basis of clinical signs. Such children usually have normal body weight and height at birth, however, already during the first year of life happen retardation in stato-kinetic, pre-speech and speech development, hypotony, general organism weakness, repeated respiratory diseases, slow weight gain, constipations and difficulties in feeding (bad sucking, shaking, swallowing difficulties) [9, 23, 24]. Some jabber sounds appear after one year of age, proper speech develops with considerable retardation, and such children do not understand for a long time the speech addressed to them, which demands special speech therapy [25, 38]. It was also noted that if such child is brought up in a family, his/her IQ is higher than in children, who are raised in boarding school. Independent walking is formed only by 1.5 — 2 years of life [36, 45].

The following characteristic changes may be noted in cases of Rubinstein—Taybi syndrome: prolonged nonclosure of large vertex, brachycephaly, protruding forehead with low hair line, wide nasal bridge, nose alae hypoplasia, high arcuate brows, epicanthus, moderate retro- or micrognathia, crevice of tongue, palate and upper lip, ear conches deformation, decrease or increase, and facial grimace or unusual smile with practically complete eyes closure. Such patients have low height. Teeth abnormalities also should be noted, such as abnormal teeth position, lateral occlusion, hypoplasia, and enamel colour changes. Virtually one half of such patients develop frequent ear infections, which may be accompanied by hearing loss. 80% of patients with this pathology have eye pathologies, such as cataract, lacrymonasal duct stenosis, and strabismus, glaucoma, and optic nerves atrophy and refraction abnormalities [15, 18, 35, 39, 43]. Therefore, such children should be examined by ophthalmologist. It should be noted that this syndrome is accompanied by interesting changes in dermatoglyphics: «three-deltoid» curls on the first fingers, arches on the second and third fingers, increased patterns density on the 2nd and 3rd digital cushions, and single palm flexural fold. *Thus, dermatoglyphic examination is integral part of geneticist examination of children with Rubinstein—Taybi syndrome*. Dermatoglyphic analysis is especially important in case of lethal pathologies of unclear aetiology, syndromal forms of intrauteral development retardation and congenital defects of unknown aetiology, congenital extremities defects and somatic asymmetry, psycho-motor development retardation of unclear genesis, and gender abnormalities [7, 10, 18]. It is notable that in Rubinstein—Taybi syndrome tumours develop more frequently, in particular such tumours as oligodendroglioma, neuroblastoma, medulloblastoma, meningioma, phaeochromocytoma, and leiomyosarcoma and naso-pharyngeal rhabdosarcoma [31, 36].

In 35–40 % of cases congenital heart abnormalities occur, such as heart septal defects, patent ductus arteriosus, and aortic coarctation [27, 40]. Among other congenital abnormalities we should note unilateral renal aplasia, kidney duplication, hydronephrosis, bladder ears, and disturbances in lungs lobulation. The majority of male patients have cry-

ptorchism, which demands appropriate surgical intervention [15, 18].

Locomotor system abnormalities include widening and shortening of nail bones of the first finger on hands and feet — 100 % of cases, sometimes — in terminal bones of other hand fingers; digital joints valgus; nail bone duplication in 1st feet fingers — in 30 % of cases, more seldom — of proximal phalanx; in some cases — feet polydactylia, partial dactylion of hand and feet fingers; knee-cup dislocation. Also are noted lordosis, kyphosis, scoliosis, sternum and ribs abnormalities, flattening of pelvic bones wings. In almost half of syndrome cases are revealed hirsutism, bright-red nevus on forehead skin, occipital and lateral neck surface, and callosities [26, 36, 44]. Average height for adult males is 153.1 cm, for adult females — 146.7 cm [41].

Among characteristic changes in Rubinstein—Taybi syndrome we should especially stress changes in central nervous system. The most frequent are congenital brain defect, such as corpus callosum agenesia. However, in literature are described rare cases of congenital Dandy—Walker malformation and Arnold-Chiari-1 malformation in cases of this syndrome [8, 28, 48]. It should be especially noted that one of corpus callosum important functions is securing inter-hemispheric slowdowning for hemispheres activity differentiation and more effective information processing. Intellect level also depends on inter-hemispheric interaction quality. Children with corpus callosum agenesia are characterized with disturbances in visual-spatial functions, difficulties in sounds location in space, bimanual tests disturbances, emotional deficit and psychological-social difficulties. Corpus callosum agenesia may play important role in epileptic seizures, developmental abnormalities and various neurological and psychic disturbances — such as autism, schizophrenia, attention deficit and hyperactivity disorder, dyslexia, etc. [4, 12, 32]. In cases of Rubinstein—Taybi syndrome there are noted changes, such as decrease of pyramidal cells count in cortex layers and slowing down of myelinisation rate, mental retardation, severe delay in expressive speech development, disturbances in movements coordination, hypotonia and epileptic seizures. Mental retardation took place in all cases, and it was predominantly of severe degree. In literature cases were described, when intellectual coefficient (IQ) was close to normal (70–80); however, it was established that in 74 % of cases IQ was less than 50 [15, 27]. Epileptic seizures happen in 20–25 % of cases, correlating with mental retardation degree. Among behavioural and psychic manifestations we should mention bad concentration, disorganization, non-critical thinking, emotional lability and restlessness, sometimes with aggression and auto-aggression, and obsessional-compulsional disturbances [27, 36, 45].

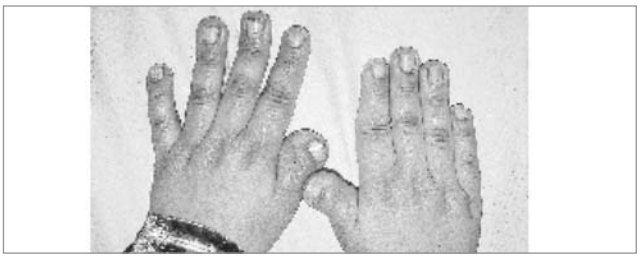

Fig. 1. Short and broad terminal first phalanxes of fingers

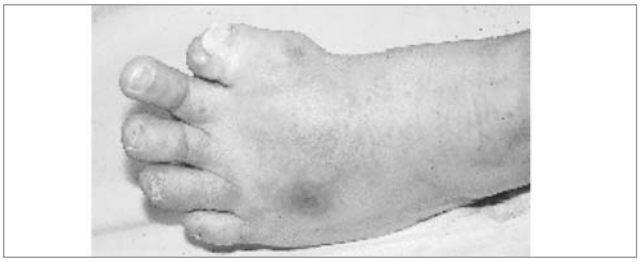

Fig. 2. Short and wide terminal phalanx of the first toe

Usually Rubinstein—Taybi syndrome diagnosis is established after birth, considering characteristic clinical changes. At that combination of facial abnormalities with wide and short hand and feet fingers is important. The most characteristic feature is nail bone widening of hands and feet (100 % of cases), which is illustrated by Fig. 1 and 2 [26].

At present there is no perfect prenatal diagnostics of Rubinstein—Taybi syndrome. There are isolated reports in literature of some cases of this pathology, when basing on prenatal sonography results Rubinstein—Taybi syndrome was suspected, considering characteristic dysmorphisms (beak-like nose, micrognathia, extremities changes with nailbones widening of the first hand and feet fingers), on the background of hydramnion. In some cases this syndrome was genetically confirmed by the method of in situ hybridization (FISH-method) after amniocentesis, in other cases genetic testing did not confirm this pathology [19]. In this connection we should mention that genetic testing not always confirms diagnosis of Rubinstein—Taybi syndrome [11, 14]. At present to discover this pathology modern molecular-cytogenetic research methods may be used, basing on chromosomes hybridization with various types of DNA-probes, or on quantitative determination of chromosome-specific marker DNA sequences: in situ hybridization (FISH-method), comparative genome hybridization on DNA-microchips (array CGH), quantitative fluorescent polymerase chain reaction, and multiplex ligase amplification (MLPA). Now genetic testing can confirm the diagnosis only in 55–60 % of patients [1, 21, 34, 49].

There are certain difficulties in prenatal diagnostics of corpus callosum agenesia, which often accompanies Rubinstein—Taybi syndrome. Corpus callosum echographic assessment by ultrasound examination is possible only after 20 weeks of pregnancy. According to the research of Volpe P. et al. [46], prenatal corpus callosum agenesia was established only in 37 % of such cases. Therefore, in case of suspicion of corpus callosum agenesia the foetus anatomical features should be closely studied to exclude accompanying defects, because this pathology is often part of syndromes with multiple and combined developmental defects, in particular, Rubinstein—Taybi syndrome. In order to specify the diagnosis, add to echography results and improve prenatal diagnostics quality in such cases magnetic resonance tomography of small pelvis (MRT) might be necessary (starting from pregnancy week 20). MRT allows examining a foetus thoroughly, and in particular studying central nervous system structures without negative effect of foetus, as well as optimizing pregnancy management tactics and delivery [5, 16, 17]. The necessary prenatal examination component is also karyotype determination.

There is no specific therapy for this syndrome, and the treatment is only symptomatic. Such patients may often require various surgical interventions, such as heart abnormalities correction and hand or feet finger bones correction.

Please, see below the description of clinical case of girl patient I., 8 years old, who underwent examination and treatment in Children Psychoneurology Department of State Institution «Institute of Pediatrics, Obstetrics and Gynaecology of the National Academy of Medical Sciences of Ukraine» with the diagnosis: «Rubinstein—Taybi syndrome, general speech underdevelopment of 1st level, cognitive functions decrease. Left renal hypoplasia. Enuresis».

The girl was admitted with complaints of pronounced retardation in psycho-speech development, defect speech; she could not read, knew not all letters, could circle with pencil simple objects contours, followed only simple instructions, and was emotionally labile.

Medical history data — the girl was from the first pregnancy, and first delivery. During pregnancy the mother suffered from abortion threat during the first trimester, and pielonephritis. Examination for TORCH-complex infections yielded negative results. During pregnancy hydramnion took place. Delivery was at 38–39 weeks, by natural way, and uncomplicated. The child body weight after birth was 3300 g, body length 52 cm, she took the breast at once; however, she sucked and swallowed with difficulties. On the 3rd day of life aspiration with further pneumonia happened. Until 1 year of life periodic episodes of «choking» and «jamming» were noted. The development was retarded. The girl started to hold the head at 3 months, to sit at 9 months, and she walked at the age of 2 years. She started to pronounce individual syllables after 4 years. She is visiting special school (for special needs children), knows not all letters, can not read, and draws (circles objects contours). Parents negate seizures. The girl often falls sick with respiratory diseases.

Neurological status — the head of microcephalic form, epicanthus, hypertelorism, wide nasal bridge, ear conches are decreased, increased intervals between teeth, micrognathia and *wide and short nail bones of the fist fingers of hands and feet*. Cerebrocranial nerves functions -divergent strabismus, n.oculomotorius paresis in the both eyes, high gothic palate. Swallowing is not disturbed. Muscle tone is decreased. Tendon reflexes, D=S. Abdominal reflexes are positive. Plantar reflexes are brisk. General speech underdevelopment of 1st degree, cognitive functions decrease, dysarthria, unstable concentration, emotional lability. Enuresis.

According to ethical considerations and girl mother refusal the patient was not photographed.

Brain magnetic resonance tomography (MRT) — conclusion: on the series of native MR-pictures near lateral ventricles triangles on the background of unchanged grey matter there are changes — MR-signal increased, identical to grey matter signal. Ventricles and subarachnoid cavities are without pathology. Rostral part of corpus callosum is hypoplastic.

Electroencephalogram (EEG) — conclusion: on the background EEG dominance of poly-frequency disorganized alpha-rhythm, periodical regional slow-downs, predominantly in occipital-frontal and parietal leads. After photo-stimulation and hyperventilation — increase of sharp wave activity, splashes of bilateral-synchronous theta and delta-waves in all leads. Pronounced dysfunction of diencephalon-stem structures.

Electrocardiogram (ECG) — conclusion: sinus rhythm, heartbeat 100 bpm, normal position of electric heart axis: 64 degrees, incomplete right bundle branch block, moderate metabolism changes in myocardium.

Ultrasound examination revealed left renal hypoplasia.

Psychiatrist consultation — conclusion: intellectual-mnestic insufficiency of threshold level. Expressive speech disturbance as general speech underdevelopment of 1st degree. Dysarthria. Enuresis. Rubinstein—Taybi syndrome.

Genetic consultation: the girl presents clinical manifestations of Rubinstein—Taybi syndrome: microcephaly, epicanthus, micrognathia, and hypertelorism, and large nose, wide and short nail bones of the fist fingers of hands and feet, physical development retardation. Signs of connective tissue dysplasia. Conclusion: Rubinstein—Taybi syndrome, autosomal dominant inheritance type, risk for children 50 %.

According to cytogenetic examination, the girl has karyotype 46 XX.

After completed examinations and treatment course the girl was discharged from hospital for neurologist and paediatrician supervision at home.

This clinical case illustrated classic case of Rubinstein—Taybi syndrome with characteristic anamnesis, neurological and somatic picture. This pathology is rare and unique, with multi-system character of various organs and organs systems disturbances, high risk of tumours formation and tendency to infectious diseases. At that the leading importance has central nervous system disturbance, accompanied by mental retardation in all cases, and various behavioural disturbances, often combined with congenital CNS malformations and epileptic seizures, which constitute the most frequent reason, why such patients turn to doctors — paediatric neurologists. Today this syndrome prenatal diagnostics is not sufficiently developed; this pathology in majority of cases is diagnosed post partum, while genetic testing at present may confirm the diagnosis only in 55–60% of patients. However, medical-genetic consultation of families that have a child with such pathology (high risk group) is obligatory, and diagnostic scheme necessary component should be aiming at repeated risk revealing and drawing of prenatal examinations program in case of further pregnancies, with foetal cells DNA-test, obtained by amniocentesis (pregnancy week 15–18) or chorionic biopsy (pregnancy week 10–12). In case of ultrasound examination the foetus anatomical features should be closely studied, considering characteristic dysmorphic changes in skull and face, locomotor apparatus, internal organs and brain abnormalities in Rubinstein—Taybi syndrome. In case of suspected congenital foetus abnormality and insufficient visualization of its anatomical structures magnetic resonance tomography of small pelvis (MRT) (starting from pregnancy week 20) has decisive meaning to establish exact diagnosis, as well as to optimize pregnancy management tactics and delivery.

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