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IMAGING IN THE DIAGNOSIS OF RARE DISEASES

OBRAZOWANIE W DIAGNOSTYCE CHORÓB RZADKICH

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Abstract

A disease is considered rare if it affects no more than 5 in 10 000 people. More than six thousand rare diseases have been detected so far and they affect 6-8% of the population which equals 2.3-3 million people in Poland. Some of the rare diseases are already diagnosed in utero, e.g. skeletal dysplasias on ultrasonography or central nervous system diseases on magnetic resonance imaging (MRI). Many cases are finally diagnosed after radiologist's suggestion in a radiological report. Although diagnostic imaging cannot be considered as a basis for diagnosis of most of rare diseases, these studies represent an important element in the diagnostic chain. The complicated and long process of diagnosis may be significantly shortened by suggestions of the radiologist, based on the observation of these elements of radiological appearance of the lesions that are characteristic for a particular group of diseases, or even for a particular disease entity. However, the absolute condition for success is the close clinical-radiological cooperation, with clinicians providing the radiologists with their knowledge of patient's history, clinical manifestations, and the results of other investigations.

Key words: rare diseases, diagnostic imaging

Streszczenie

Choroba jest uważana za rzadką, jeżeli dotyczy nie więcej niż 5 osób na 10 000. Do tej pory opisano ponad 6 tysięcy chorób rzadkich, występują one u 6-8% populacji, co w Polsce stanowi 2,3-3 mln osób. Niektóre z tych chorób są rozpoznawane już w życiu płodowym, np. dysplazje szkieletowe w ultrasonografii, a choroby ośrodkowego układu nerwowego w rezonansie magnetycznym (MR). Wiele przypadków jest ostatecznie rozpoznawanych po sugestii radiologa w opisie badania. Mimo że badania obrazowe nie mogą być uważane za podstawę rozpoznania większości chorób rzadkich, to badania te stanowią ważny element łańcucha diagnostycznego. Skomplikowany i długotrwały proces diagnostyczny może być znacznie skrócony dzięki sugestiom radiologa, opartym na obserwacji tych elementów obrazu zmian, które są charakterystyczne dla danej grupy chorób lub nawet danej jednostki chorobowej. Jednak nieodzownym warunkiem sukcesu jest ścisła współpraca kliniczno-radiologiczna i dostarczenie radiologowi danych z wywiadów, o objawach klinicznych oraz wyników innych badań dodatkowych.

Słowa kluczowe: choroby rzadkie, diagnostyka obrazowa

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INTRODUCTION

More than six thousand rare diseases have been detected so far, and new entities are regularly described in the medical literature. In the wake of the definition of rare diseases recommended by the European Union, a disease is considered rare if it affects no more than 5 in 10 000 people. It is estimated that these diseases affect 6-8% of the population. Taking into account Polish demographic data it turns out that 2.3-3 million people suffer from rare diseases in Poland. Therefore every specialist at some moment of his/her professional life may face a patient

with unexplained ailments who will finally be diagnosed with such a disease. This concerns also a radiologist due to clinicians' growing demand for imaging studies.

One should take into account that rare diseases are not commonly known even to medical community because of their rarity and diversity. Therefore every educational effort aiming to spread knowledge about these diseases is a valuable initiative [1] in line with the motto on the website of Orphanet: "There is no disease so rare that it does not deserve attention".

EXPERIENCE OF THE DEPARTMENT OF DIAGNOSTIC IMAGING OF THE INSTITUTE OF MOTHER AND CHILD IN WARSAW

It would be very difficult to quantify our expertise in imaging of rare diseases, because there are so many of them and we studied often one patient with a particular disease, beginning with the fetuses but certainly the material of 19 years of work with patients with rare diseases would include hundreds of such studies.

Thanks to the dynamic development of magnetic resonance techniques the age of our patients has shifted to the prenatal group. Fetal ultrasonography (US) is usually performed by gynecologists but radiologists started to be involved in the prenatal diagnostics over thirty years ago in the world and approximately 16 years ago in Poland when magnetic resonance imaging (MRI) became a diagnostic method in this period of human life. Our Institute is the leading centre of prenatal MRI in Poland. Some of the rare diseases are already diagnosed *in utero*, e.g. achondroplasia or bony dysplasias. Shortened limbs, deformed skull or chest bones (fig. 1a, b, c) indicate one of these diseases. Many of them are lethal but even in a stillborn baby an x-ray should be performed to determine the type of dysplasia, which is a very important element of counseling on possible future pregnancies of the couple. In case of skeletal dysplasias these are the gynecologists who first discover the abnormalities which are well seen on US, while as far as the fetal central nervous system is concerned no method can be compared with the MR examination. Especially the midline structures, posterior cranial fossa and cerebral cortex are "resistant" to US. Therefore only MRI allows for early recognition of numerous rare diseases and syndromes – for example in our material we have a case of Walker-Warburg syndrome diagnosed as early as at the gestational age of 22 weeks. This syndrome the prevalence of which is estimated at 1:60 500 is extremely difficult to recognize so early because lissencephaly is one of its key features and fetal brain is physiologically "lissencephalic" at 22 gestational weeks. But the coexistence of ventriculomegaly, Dandy-Walker variant and kinked brainstem (fig. 2a, b) raised the suspicion of this rare syndrome [2] which was confirmed after birth since the parents did not wish to terminate the pregnancy.

However in many cases the radiological appearance of a lesions is so unspecific that the diagnosis by no means can be established on the basis of imaging alone.

For example we examined a fetus with a huge cyst in the abdomen (fig. 3a) – without the final diagnosis on prenatal MRI: any cystic lesion from the long list of possible entities should have been taken into consideration. After birth we examined this newborn in the MR-compatible

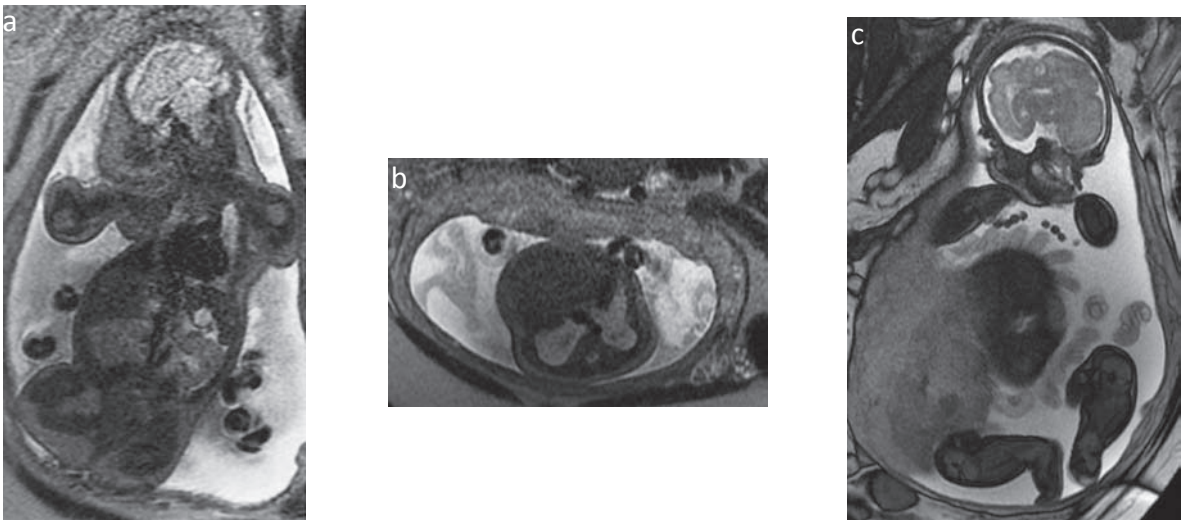

Fig. 1. A fetus at the gestational age of 32 weeks with skeletal dysplasia: Narrow chest (a), concavity of ribs (b) and shortened limbs (c).

Ryc. 1. Płód z dysplazją szkieletową, badany w wieku ciążowym 32 tygodni. Widoczna jest wąska klatka piersiowa (a), wklęsły zarys żeber (b) i skrócenie kończyn (c).

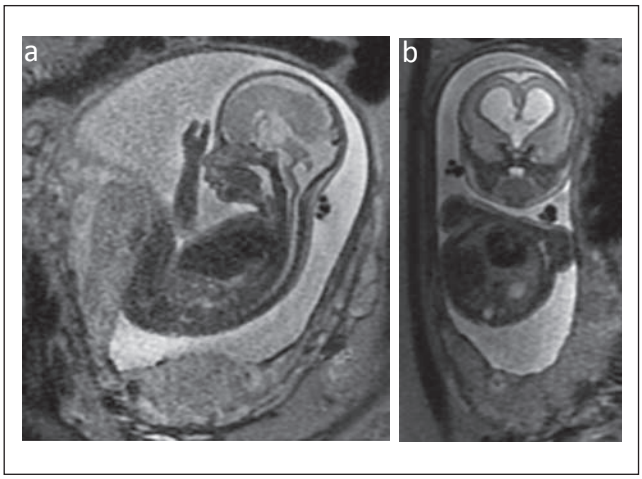

Fig. 2. A fetus at 22 gestational weeks. The picture of Dandy-Walker variant, brainstem kinking (a) and ventriculomegaly (b) led to the early diagnosis of Walker-Warburg syndrome.

Ryc. 2. Płód w wieku ciążowym 22 tygodni. Obraz wariantu Dandy-Walkera, wygięcia pnia mózgu (a) oraz wektrikulomegalii (b) pozwolił na bardzo wczesne rozpoznanie zespołu Walkera-Warburga.

incubator and found not only this cyst but also numerous, tiny, enhancing lesions disseminated in the liver, diaphragm and chest wall (fig. 3b). The suspicion of neoplastic tumour with metastases seemed to be the most probable in this case although numerous hemangioma-like lesions were visible in her skin as well. After surgery the pathologic diagnosis was blue rubber bleb nevus syndrome – an extremely rare vascular malformation disorder with cutaneous and visceral lesions that are frequently associated with serious, potentially fatal bleeding and anemia. Up to 2008 more than 200 cases have been published in the world, but the prevalence is unknown. Our patient's lesions turned to be venous malformations and not solid neoplastic tumours. In view of over 6000 possible rare diseases it is simply impossible to know all of them and to include them in differential diagnosis in all cases. As a rule of series a few months later we had a second case of this rare syndrome in a fetus, this time with the main tumor mass deriving from the tongue. Searching in Pubmed for the key words: "blue rubber bleb nevus syndrome", "fetus" and "MRI" one finds no results.

The importance of imaging is very large for rare diseases, both during the diagnostic process of a suspected rare disease and in situations when clinically such a suspicion had not yet been defined but taking into consideration the clinical symptoms – the patient is already referred for imaging. In our rich material we have the examples of rare diseases which have been finally diagnosed after radiologist's suggestion in MRI report. These examples include among others X-linked adrenoleukodystrophy (X-ALD) or neuronal ceroidolipofuscinosis (NCL). In view of vague history and general poor condition of the boy, the characteristic picture of white matter changes in the posterior parts of the brain, including the corpus

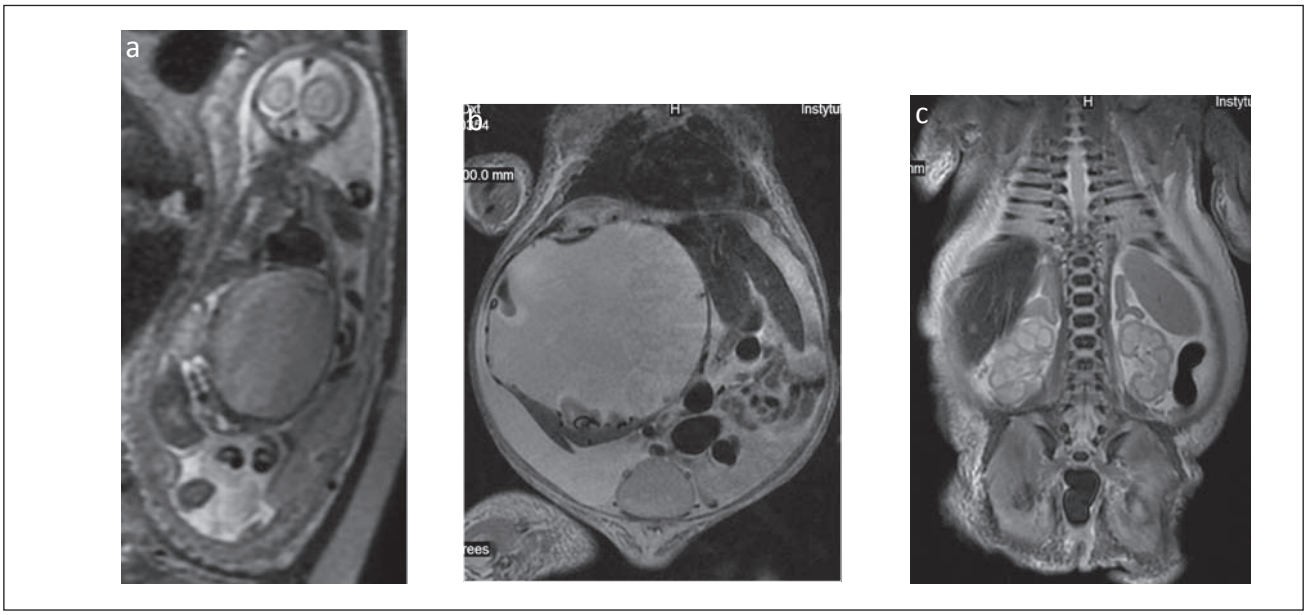

Fig. 3. Blue rubber bleb nevus syndrome in a 25-week fetus (a) and in a newborn on the second day of life (b,c). The huge abdominal and pelvic cyst could have been properly named neither on the basis of fetal MRI (a) nor on postnatal examination (b,c). The additional nodules (here in the right lobe of the liver – c) suggested diagnosis of a malignant tumour with metastatic spread.

Ryc. 3. Zespół gumiastych pęcherzyków znamionowych u 25-tygodniowego płodu (a) i u noworodka w drugiej dobie życia (b, c). Olbrzymia torbiel wypełniająca jamę brzuszną i miednicę nie mogła być właściwie rozpoznana ani w płodowym badaniu MR (a), ani po urodzeniu (b, c). Dodatkowe guzki (tu w prawym płacie wątroby – c) sugerowały rozpoznanie złośliwego guza z przerzutami.

callosum, had raised the obvious suspicion of X-ALD which was later confirmed (fig. 4) [3]. Unclear clinical picture, normal previous brain MRI and generalized brain atrophy six months later were the reasons to suggest NCL. This radiological suggestion was also confirmed.

In most cases however diagnostic imaging is one of numerous investigations that are undertaken with a suspicion of a rare diseases in mind. The cooperation of the clinicians and the radiologist is one of key elements in reaching the correct diagnosis in these cases. In many of them the clinical picture is unclear and radiological appearance is nonspecific. Joint discussion of the involved specialists on the patient is essential to resolve the issue. The diagnostic difficulties resulting from lack of clinical-radiological cooperation may delay the proper diagnosis. We described such difficulties in our two patients with Krabbe disease [4].

In a multidisciplinary team including the paediatrician, paediatric neurologist, radiologist and clinical geneticists the ability to associate the findings from various imaging and laboratory studies, clinical picture and continuously appearing new descriptions of the entities of a group of rare diseases is increased and leads to a proper diagnosis as it was in our case of the first Polish patient with 4H syndrome [5]. White matter hypomyelination on brain MRI and hypodontia on orthopantomogram as well as the clinical picture of mental retardation and hypogonadism were the clue in this case.

In many rare diseases multiple radiological examinations of various parts of the body are used to establish diagnosis. For example in neonatal Zellweger syndrome brain MRI shows neuronal migration abnormalities and white matter hypomyelination (fig. 5), x-rays: chondrodysplasia punctata (punctate calcifications of the cartilage), and US – renal cysts.

Imaging plays also a role that is impossible to overestimate in emergency cases. These include not only trauma or stroke but also, among others, some rare diseases that present as acute incidents. The example is maple syrup urine disease in a comatose newborn or acute exacerbation in Leigh syndrome. The disease is not always diagnosed earlier and the baby may be admitted to the hospital due to acute symptoms of an undiagnosed entity. In such a case from our material a shortened MRI protocol lasting for about 15 minutes was sufficient to establish diagnosis. Axial FSE/T2-weighted images, diffusion-weighted sequence (DWI) and single voxel proton spectroscopy (1H MRS) with both a short and long echo time gave the practically definite diagnosis of Leigh syndrome in our patient. Typical symmetrical lesions in deep structures of both cerebral hemispheres as well as in brainstem with restricted diffusion and double lipid/lactate peak were diagnostic (fig. 6a, b, c, d) [6]. The interdisciplinary team decided to forgo the treatment, which in this case would carry the signs of aggressive medical treatment, and to introduce palliative care only.

The cases described above concern the children, since about half of the rare diseases are disclosed in childhood. Creutzfeldt-Jacob disease (CJD) is a good example of such a disease in adults and of the extremely important role of MRI in the diagnosis. Not only the inborn diseases are

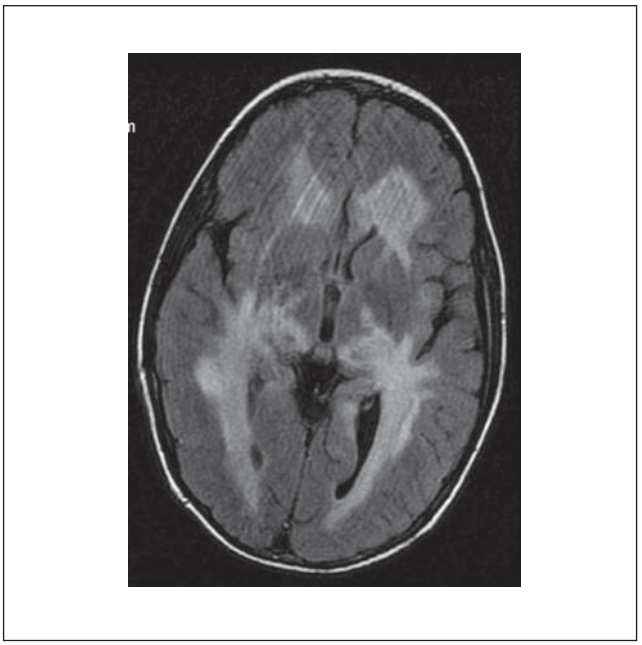

Fig. 4. A 10-year-old boy with a characteristic MR appearance of X-linked adrenoleukodystrophy which was confirmed after MRI.

Ryc. 4. 10-letni chłopiec z charakterystycznym obrazem MR adrenoleukodystrofii sprzężonej z chromosomem X, która została potwierdzona po badaniu MR.

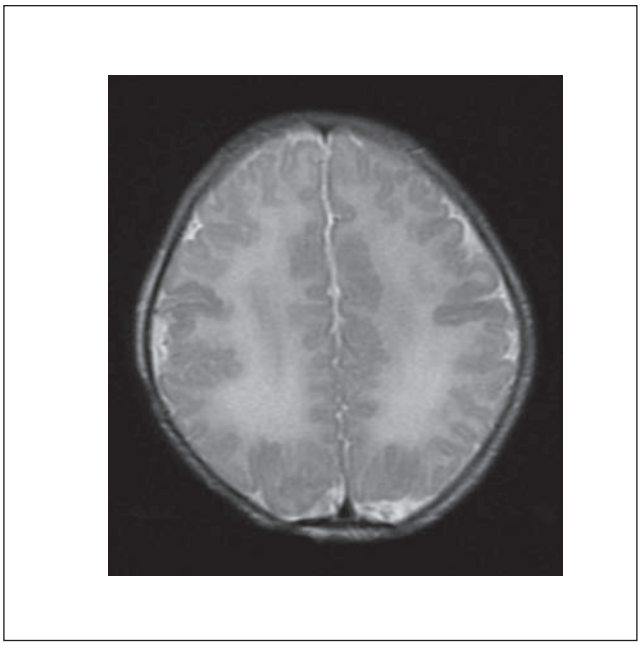

Fig. 5. A 9-day-old boy with neonatal Zellweger syndrome. White matter hypomyelination and bilateral polymicrogyria.

Ryc. 5. Dziewięciodniowy chłopiec z noworodkowym zespołem Zellwegera. Hipomielinizacja istoty białej i obustronna drobnozakrętowość.

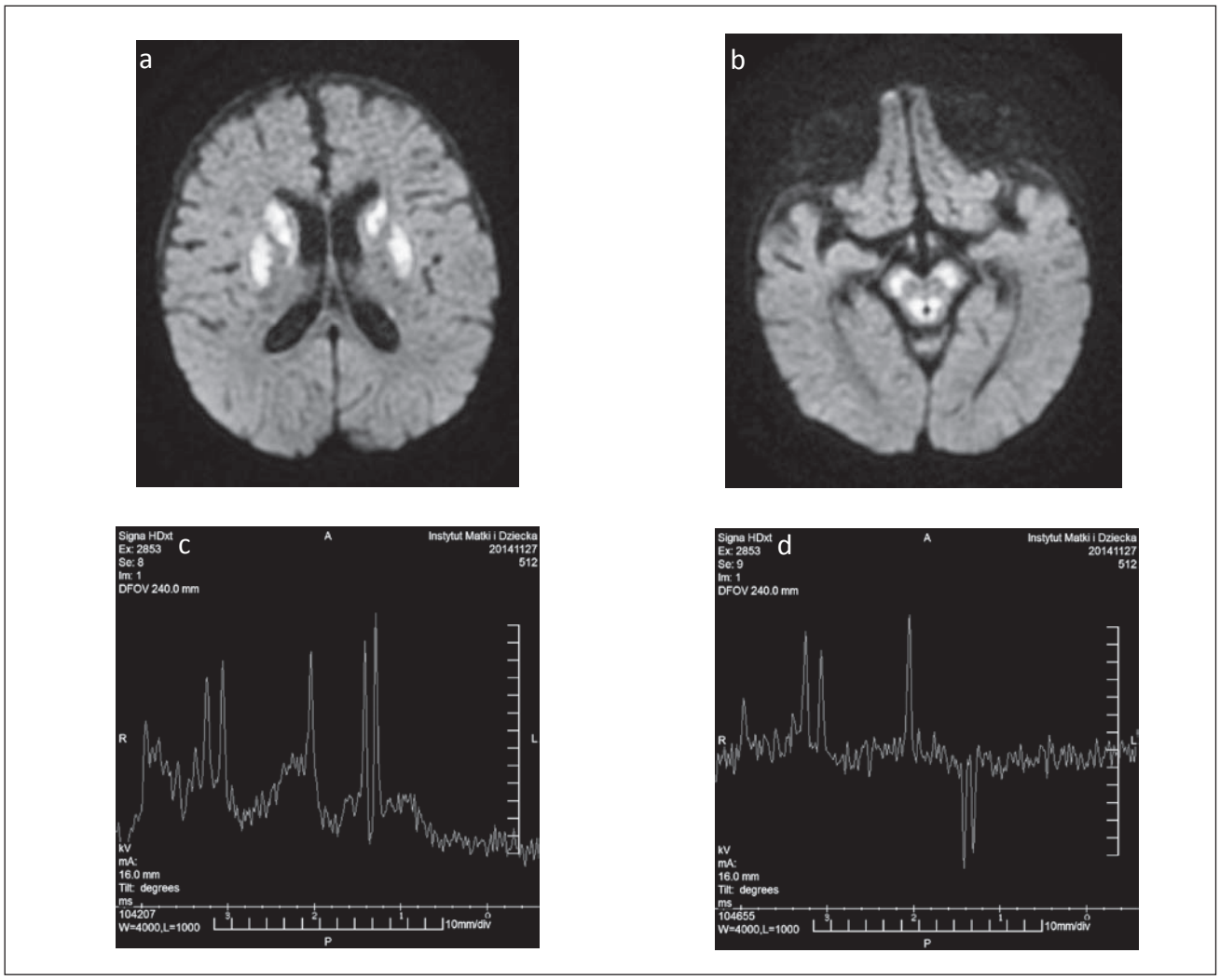

Fig. 6. A 7-month-old boy with typical MRI picture of Leigh syndrome: restricted diffusion in the basal ganglia (a) and brainstem (b). Proton MR spectroscopy shows very high peak of lactate at 1.39 ppm with a short echo time of 35 ms (c) which is inverted when the long echo time of 144 ms is used (d).

Ryc. 6. 7-miesięczny chłopiec z typowym obrazem MR zespołu Leigha: ograniczenie dyfuzji wody w jądrach podstawy mózgu (a) i pniu mózgu (b). Protonowa spektroskopia MR z krótkim czasem echa (TE = 35 ms) uwidacznia w pozycji 1,39 w skali ppm bardzo wysoki dublet mleczanów (c), który ulega odwróceniu po zastosowaniu długiego czasu echa (144 ms) (d).

included in the rare diseases list - the criterion is occurrence in the population no more frequent than 5:10 000. MRI appearance of CJD with gyral and striatal FLAIR and DWI hyperintensities is so distinctive that it has been incorporated into the diagnostic criteria of the disease, in addition to the clinical and electroencephalographic (EEG) findings [7].

Probably the bible for many physicians dealing with rare diseases involving the brain is a book by van der Knaap and Valk [8]. The authors give there a list of diseases that have diagnostic, highly suggestive and suggestive appearance on MR imaging. In my opinion, after 19 years of work with patients with rare diseases, this list could be extended and include at least a few more entities like Menkes disease, leukoencephalopathy with vanishing white matter (VWM), leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL) [9, 10].

Finally, not to be underestimated is the role of imaging in the development of knowledge about rare diseases. Given their diversity and rarity, any further description of the case can bring new, relevant information on the disease, with each new case we learn more about it. Our material includes, among others, a description of adenylosuccinate lyase (ADSL) deficiency, which proved that in this disease we deal not only with the reduced myelination and progressive atrophy of the brain which has been believed so far but also with demyelination of previously normal white matter, correlating with clinical deterioration [11]. Therefore in addition to practical clinical use, imaging plays also, of course, an important scientific role.

CONCLUSION

Although diagnostic imaging cannot be considered as a basis for diagnosis of most of rare diseases, these studies represent an important element in the diagnostic chain. The complicated and long process of diagnosis may be significantly shortened by suggestions of the radiologist, based on the observation of these elements of radiological appearance of the lesions that are characteristic for a particular group of diseases, or even for a particular disease entity. However, the absolute condition for success is the close clinical-radiological cooperation, with clinicians providing the radiologists with their knowledge of patient's history, clinical manifestations, and the results of other investigations.

REFERENCES

1. Bekiesińska-Figatowska M, Jurkiewicz E, Wagiel K, Kmieć T. Miejsce rezonansu magnetycznego w łańcuchu diagnostycznym wrodzonych chorób istoty białej i innych zwyrodnieniowych chorób ośrodkowego układu nerwowego u dzieci. Neurologia Dziecięca 2005;14:37-45.
2. Strigini F, Valleriani A, Cecchi M, Ghirri P, Aiello C, Bertini E, Cioni G, Battini R. Prenatal ultrasound and magnetic resonance imaging features in a fetus with Walker-Warburg syndrome. Ultrasound Obstet Gynecol 2009;33:363-365.
3. Engelen M, Kemp S, de Visser M, van Geel BM, Wanders RJ, Aubourg P, Poll-The BT. X-linked adrenoleukodystrophy (X-ALD): clinical presentation and guidelines for diagnosis, follow-up and management. Orphanet J Rare Dis. 2012;7:51.
4. Szymańska K, Ługowska A, Laure-Kamionowska M, Bekiesińska-Figatowska M, Gieruszczak-Białek D, Musielak M, Eichler S, Giese A-K, Rolfs A. Diagnostic difficulties in Krabbe disease: a report of two cases and review of literature. Folia Neuropathol. 2012;50:346-356.
5. Bekiesińska-Figatowska M, Mierzewska H, Kuczyńska-Zardzewiały A, Szczepanik E, Obersztyn E. Hypomyelination, hypogonadotropic hypogonadism, hypodontia - first Polish patient. Brain Dev. 2010;32:574-578.
6. Saneto RP, Friedman SD, Shaw DW. Neuroimaging of mitochondrial disease. Mitochondrion. 2008;8:396-413.
7. Bekiesińska-Figatowska M, Kuczyńska-Zardzewiały A, Pomianowska B, Kajdana K, Szpak G, Iwanowska B, Mądzik J. The value of magnetic resonance imaging in the early diagnosis of Creutzfeldt-Jakob disease – own experience. Pol J Radiol. 2012;77(1):68-71.
8. van der Knaap MS, Valk J. Magnetic resonance of myelination and myelin disorders. Springer-Verlag Berlin Heidelberg 2005.
9. Jurkiewicz E, Mierzewska H, Bekiesińska-Figatowska M, Pakuła-Kościesza I, Kmieć T, Scheper G, van der Knaap MS, Pronicka E: Magnetic Resonance Imaging of Leukoencephalopathy with Vanishing White Matter – Family Report. Pediatr Radiol. 2005;35:1027-1030.
10. Mierzewska H, van der Knaap MS, Scheper GC, Bekiesińska-Figatowska M, Szczepanik E, Jurkiewicz E. Leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation in the first Polish patient. Brain Dev. 2011;33:713-717.
11. Bekiesińska-Figatowska M, Szymańska K, Schmidt-Sidor B, Mierzewska H, Bogdańska A, Kuśmierska K, Romaniuk-Doroszewska A. Novel MRI and clinical findings in a boy with adenylosuccinate lyase deficiency. Eur J Radiol Extra. 2009;71:e3-e5.

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