APPROACHES TO THERAPY OF CRIGLER–NAJJAR SYNDROME TYPE 1 IN CHILDREN

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The review is focused on exploring the etiology, pathogenesis, clinical manifestations, and primarily the contemporary treatment methods for Crigler–Najjar syndrome type 1. It considers relevant data regarding the efficacy and safety of the currently existing therapeutic strategies. Effective management of this condition relies on early diagnosis and prompt initiation of treatment, which are crucial for preventing disabling neurological complications associated with bilirubin encephalopathy in patients with Crigler–Najjar syndrome type 1. Prolonged phototherapy is the key treatment method, while liver transplantation represents a radical approach. Recent advances in gene therapy and the use of mesenchymal multipotent stromal cells present novel opportunities for developing alternative, less invasive treatment modalities aimed at improving the quality of life in such patients and reducing their dependence on long-term phototherapy, along with post-transplantation risk.

Keywords: Crigler–Najjar syndrome type 1, indirect hyperbilirubinemia, nuclear icterus, phototherapy, liver transplantation, gene therapy

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ПОДХОДЫ К ТЕРАПИИ СИНДРОМА КРИГЛЕРА–НАЙЯРА 1-ГО ТИПА У ДЕТЕЙ

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Обзор посвящен изучению этиологии, патогенеза, клинической картины и, прежде всего, современных методов лечения синдрома Криглера–Найяра (СКН) 1-го типа. Рассмотрены актуальные данные об эффективности и безопасности существующих терапевтических стратегий. Эффективная терапия данного заболевания основана на ранней диагностике и незамедлительном начале лечения, что критически важно для предотвращения инвалидизирующих неврологических осложнений, связанных с билирубиновой энцефалопатией у пациентов с СКН 1-го типа. Ключевым методом лечения является продолжительная фототерапия, а радикальной мерой — трансплантация печени. Последние достижения в области генной терапии и использования мезенхимальных мультипотентных стромальных клеток открывают новые возможности для разработки альтернативных, менее инвазивных методов лечения, направленных на улучшение качества жизни пациентов с этим заболеванием и снижение их зависимости от длительной фототерапии и послеоперационных рисков, связанных с трансплантацией печени.

Ключевые слова: синдром Криглера–Найяра 1-го типа, непрямая гипербилирубинемия, ядерная желтуха, фототерапия, трансплантация печени, генная терапия

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Crigler–Najjar syndrome (CNS) is a rare autosomal recessive inherited disorder characterized by impaired conjugation of bilirubin in the liver caused by lack or low level of the uridine diphosphate glucuronosyltransferase (UGT) enzyme, which leads to the development of nonhemolytic jaundice.

Etiology

The *UGT1A1* gene encoding the UGT enzyme plays a key role in conjugation of indirect bilirubin. Mutations in the *UGT1A1* gene can completely arrest or hamper the activity of this enzyme, which translates into hyperbilirubinemia. Depending on the degree of decrease in enzyme activity, CNS is classified into types 1 and 2 (CNS1 and CNS2). In CNS1 cases, there is no enzyme activity, and therefore, without treatment, the disease causes severe neurological disorders due to bilirubin encephalopathy. In CNS2 cases, the level of bilirubin in the blood serum is high, but, as a rule, there is no progression to neurological disorders.

CNS1 is extremely rare: its incidence is about 0.6–1 case per 1 million live newborns worldwide, and less than one per 100,000 newborns in Europe [1, 2]. There are no prevalence specifics in terms of sex and ethnicity, but it is known that CNS1 is diagnosed more often in genetically isolated populations, such as communities of Old Believers and Mennonites, as well as among children born to parents in a related marriage [3, 4].

The CNS1 phenotype can occur due to various changes in the coding sequences of the bilirubin uridine diphosphate glucuronosyltransferase (*UGT1A1*) gene, such changes conditioning formation of an abnormal protein that fully arrests or disrupts the activity of the enzyme. This cause-effect relationship makes CNS1 different from the Gilbert's syndrome, when the triggering defect is in the promoter region rather than in the gene itself, and the result thereof is a smaller amount of synthesized normal enzyme [5]. The *UGT* gene is expressed in many isoforms, but UGT1A1 is the only one that significantly contributes to bilirubin conjugation in humans. Deletions, insertions, missense mutations, or premature stop codons

in the *UGT1A1* gene can be located in any of the five exons that make up the *UGT1A1* mRNA. Genetic changes in exon 1 affect only the activity of bilirubin UGT isoform (*UGT1A1*), while mutations in exons 2-5, contrarily, affect all isoforms expressed from the UGT1A locus [6].

Clinical picture

The manifestation of the CNS1 syndrome is jaundice caused by a high level of unconjugated bilirubin. It usually appears on the second or third day of life, when the bilirubin level exceeds 85 μmol/l. Subsequently, it progressively increases and reaches 340–500 μmol/l in the first 10 days of life, and in severe cases the said level rises to 850 μmol/l. The probability of development of bilirubin encephalopathy is the highest in the early neonatal period, when the blood-brain barrier is more permeable. Total serum bilirubin and the bilirubin/albumin ratio are the indicators used to assess the risk of neurological complications. For children older than 1 month, the total serum bilirubin level above 510 μmol/l and the bilirubin/albumin ratio exceeding 1.0 mol/mol are considered the absolute thresholds of neurotoxicity [3, 7]. In the neonatal period, the threshold level of bilirubin depends on a combination of factors: gestational and postnatal age and the condition of the child. Untreated, CSN1 leads to acute bilirubin encephalopathy, kernicterus, and persistent cognitive disorders. The symptoms of CNS damage associated with CNS1 include altered state of consciousness, changes in muscle tone, hearing loss, etc. There is a report describing a case of late diagnosing of CNS1 that progressed into severe neurological disorders in the form of spastic tetraparesis [8]. In another clinical case, neurological disorders were detected in a 4-month-old child suffering from CNS1; they manifested as neurodevelopmental delay and focal structural epilepsy [9]. Kernicterus is a consequence of deposition of bilirubin in brain cells, mainly in the basal ganglia, globus pallidus, hippocampus, subthalamic nucleus, horn of Ammon, cranial nerve nuclei, and cerebellum. Choreoathetoid cerebral palsy, high-frequency central sensorineural hearing loss, vertical gaze palsy, and enamel hypoplasia are the main markers of kernicterus [10]. It is important to note that bilirubin encephalopathy can also occur in adolescents or adults, so a broader term, kernicterus spectrum disorder, was coined, and it combines the diagnoses based on clinical and pathophysiological criteria [4, 11, 12]. There is a report covering 239 cases of CNS1 and describing the various outcomes of the disease, including the high risk of bilirubin encephalopathy and other serious complications. The authors note that in 45% of patients, the disease progresses into brain damage, 27% require liver transplantation, and in 19% of cases the treatment involved exchange transfusion or plasmapheresis [3].

Historically, CNS1 was regarded as indirect hyperbilirubinemia without damage to liver tissue. However, recent reports indicate that liver fibrosis is registered in 40–60% of patients that need liver transplantation because of this disease, and the degree of fibrosis correlates with bilirubin concentration and age. Liver biopsies sampled during liver transplantation in 22 patients with CNS1 showed varying degrees of fibrosis in 41% of them in the absence of clinical and laboratory findings suggestive of liver cirrhosis and portal hypertension [13].

The quality of life in CNS1 cases can be significantly low both for the patients and for the caregivers. Patients require 10–12 hours of phototherapy per day from the first days of life [14]. Although it is a non-invasive and simple treatment method, phototherapy has a noticeable effect on the lifestyle of the family, imposing social restrictions and a heavy burden on patients and their caregivers [15]. Liver transplantation is a radical treatment method, but it carries the risks associated with donor selection, potential transplant rejection, and the need for lifelong immunosuppressive therapy.

A special problem is that of pregnancy hyperbilirubinemia with CNS1 in the background. This condition implies a risk of kernicterus in the fetus due to a high level of bilirubin in the mother. Unconjugated bilirubin passes through the placenta by passive diffusion [15]. The recommended treatment protocol prescribes monitoring and phototherapy the duration of which ensures a maternal bilirubin level below 200 μmol/l and a bilirubin/albumin ratio less than 0.5 mol/mol [16]. There is evidence of successful phototherapy in the first trimester and phenobarbital in subsequent trimesters given with the aim to maintain safe bilirubin levels in pregnant women with type CNS2 [17]. There is also experience of management of newborns from women with CNS1 who required blood transfusions after birth; one of them was diagnosed with sensorineural hearing loss at 7 months, despite phototherapy and albumin infusion the mother underwent during pregnancy [18].

Diagnostics

Prevention of neurological complications of kernicterus requires diagnosing CNS1 at early stages. Differential diagnosis involves other causes of unconjugated hyperbilirubinemia, such as jaundice caused by breast milk composition, polycythemia, systemic diseases, and other hereditary disorders of bilirubin metabolism. The key difference between CNS1 and CNS2 is the ultimate level of bilirubin, although in the first weeks of life, the respective thresholds that mark brain damage may coincide for these two conditions. A phenobarbital test helps to diagnose the disease: in CNS2 cases, this drug pushes blood bilirubin down by about 25%, but has no such effect in patients with CNS1.

Molecular genetic study can confirm or disprove a CNS diagnosis; it is designed to seek pathogenic variants in the *UGT1A1* gene encoding the enzyme enabling bilirubin conjugation. CNS1 can stem from various genetic defects, including missense and nonsense mutations, insertions, deletions, and splicing disorders affecting any of the five exons of the *UGT1A1* coding region. Therefore, it is important to sequence not only all exons, but also flanking introns, using targeted Sanger sequencing or next generation sequencing [19]. CNS1 is associated with more severe mutations, including premature stop codons, frameshift or missense mutations (substitution of one amino acid), which stop the activity of the UGT enzyme completely. CNS2, on the contrary, is typically linked to missense mutations that reduce the catalytic activity of the enzyme, but do not fully arrest it. If a patient with CNS2 also has a *UGT1A128* type promoter mutation, characteristic of Gilbert's syndrome, decreased enzyme expression can make hyperbilirubinemia even more pronounced [15, 20, 21].

Treatment

Currently, there are various approaches to the treatment of CNS1. Below, we are describing the most common and best studied of them.

The approaches to treatment of unconjugated bilirubinemia in the neonatal period with CNS1 in the background are similar to those practiced for other causes of indirect hyperbilirubinemia. Under the current clinical recommendations, phototherapy and/or exchange transfusion are prescribed when the total serum bilirubin level reaches certain threshold values.

Phototherapy

Phototherapy (PT) is the first choice against CNS1, especially for babies and children. It can significantly alter the course of the disease. PT works by converting bilirubin IX-alpha-ZZ into its configuration isomers (for example, lumirubin), which can then be excreted in bile without conjugation [22]. Although PT has been used in the treatment of indirect hyperbilirubinemia for many decades, it should be noted that the first recommendations describing how to apply it effectively in CNS cases were published only in June 2020. They detail what light source should be used, what is the optimal distance between the said source and the skin, how much of the skin should be exposed to the light, and for how long [3]. Whenever a newborn exhibits high serum bilirubin content, it is best to initiate treatment as soon as possible. If exchange transfusion is necessary, PT should be started thereafter. The average duration of the PT sessions is 12.4 ± 0.8 hours per day, including nighttime. Various PT systems deliver high-intensity radiation to large areas of the body, but their effectiveness decreases during puberty due to a number of factors (skin thickening, increased pigmentation, decreasing body surface area to body weight ratio). At the same time, adolescent patients are at a high risk of bilirubin levels spiking to critical values that imply the possibility of development of neurological disorders. For them, it is necessary to consider alternative or auxiliary treatments [3, 23].

Although PT is effective against bilirubin level abnormalities, it has its side effects. One review discusses PT as a treatment for hyperbilirubinemia in neonates, evaluating its effectiveness and potential risks, including impacts on the immune system, and the development of tumors, nevi, and allergies. [24]. There is reported evidence confirming the PT's capability to change the levels of cytokines in the blood of newborns. There is also data showing that with 24-hour sessions of PT in the background, the level of interleukin 6 (IL6) drops [25]. Other studies report growing levels of IL2 and IL10, and decreasing level of IL1b. PT was also shown to affect the amount and activity of leukocytes. A number of studies indicate a temporary growth of leukocyte levels, but these changes fade over time and have no clinical significance. The authors present evidence that PT can affect the level of antibodies and immunoglobulins in the newborn's body. Light waves of a certain length can cause structural changes in bilirubin molecules, turning them into more soluble forms that are easier to eliminate from the body. This can have an indirect effect on the metabolism of proteins, including antibodies and immunoglobulins. PT can also alter cellular metabolism, which entails modification of the processes of proliferation and differentiation of cells, including those involved in the production of antibodies and immunoglobulins [26, 27].

There is also evidence that PT may be associated with an increased risk of neoplasms in children. Two large cohort studies were conducted in California, and they found a link between PT in infancy and subsequent acute myeloid leukemia (AML) in children: this therapy raised the risk of the disease [28]. Other studies, however, have not confirmed the association of PT with a high risk of cancer. For example, there is no established connection between PT and the development of melanoma or other skin cancers, same as there is no convincing evidence of PT increasing the risk of basal cell carcinoma or squamous cell carcinoma [29]. Thus, the effect of PT on tumor development remains a controversial issue that requires further investigation.

There are studies showing that children who received PT in the neonatal period may be at a higher risk of developing allergies, including bronchial asthma and pollinosis [30, 31].

The high risk of gallstone formation associated with CNS deserves a special note. There are no published papers pointing to a connection between PT and cholelithiasis, however, it can be assumed that such a connection is possible, and it is caused by the active conjugation of bilirubin under the influence of PT, dehydration, and, as a result, a high probability of bile sludge. Normally, the level of urobilin in bile is very low, however, with PT in the background, water-soluble isomers of urobilinogen are released into the bile, and some of them can be converted back into urobilin, which forms crystals participating in the aggregation of gallstones. A worldwide cohort study claims the incidence of gallstone disease among CNS patients is at least 15% [2], and other authors report its occurrence in up to 41% of cases [3].

Gene therapy

In CNS cases, gene therapy is aimed at correcting the function of the mutated gene by achieving stable expression of the functional copy thereof. Currently, this form of treatment is enabled by viral vectors, with adeno-associated virus (AAV) vectors being best for intracellular gene therapy. The efficacy of AAV-mediated gene therapy was confirmed in preclinical models and in clinical settings involving treatment of hemophilia type A and B. Consequently, FDA has approved Valoctocogene roxaparvovec as a drug for hemophilia A [32]. One study has shown that vectors based on the adeno-associated virus effectively transduce liver cells in cell culture as well as in animal models, including mice and rats. Moreover, introduction of these vectors was demonstrated to lead to normalization of bilirubin levels in the blood of animals with CNS. Preclinical studies dedicated to the safety and effectiveness of AAV vectors included an analysis of the immune response and biodistribution, which has shown that such vectors mainly accumulate in the liver, spleen, and lymph nodes, as per their tropism towards these organs following an intravenous administration. Several months after the injection, some vector particles were found in the gonads. These data signal the need for careful monitoring of the potential risk of gene transmission through reproductive cells. Overall, the findings confirm that AAV vectors are a safe and effective CNS therapy component, and their practical application requires clinical trials [33]. There have been published data on the efficacy of gene therapy in adult patients with CNS1, which confirm it can decrease the level of bilirubin to the values below the neurotoxic threshold; the effect is persistent, and allows partial or even complete cancellation of PT. The study also investigated safety and efficacy of a single intravenous infusion of an AAV vector. The participants of the experiment were five adults with CNS1; three of them received a higher dose, and the level of bilirubin in them dropped below 300 μmol/l (17.5 mg/dl), which allowed canceling PT for the follow-up period of 18 months. However, no subject had the bilirubin level completely returned to normal [34]. Although gene therapy is promising against CNS1, there are doubts about its long-term efficacy and safety. Indeed, it is yet unclear how long does the effect of a single administration of an AAV-transgenic vector persists [35]. The effectiveness of a vector drug is mainly hampered by the produced antibodies that neutralize AAV and, consequently, impose limitations on further introduction of vectors [36]. In the preclinical rat and mice studies, all animals developed a significant immune response to the AAV capsid, and some of them produced antibodies to the *UGT1A1* protein. Searching for the source of this immune response, the researchers have set up experiments using vectors carrying the *UGT1A1* transcripts from different species (mouse and rat

variants), and have thus learned that antibodies against the human *UGT1A1* variant are formed less frequently when using species-specific variants. It is possible that species-specific transcripts decrease the immunogenicity of vectors [33]. In addition to the above, multiple infusions of AAV vectors pose a potential genotoxicity threat [37]. A study that investigated how antibodies to the AAV vector affect the effectiveness of gene therapy against CNS1 has shown that about a third of patients have these antibodies, and that when their level is low, the barrier set b them can be overcome by using the vectors with both full and empty capsids [38]. The issue of suppression of the humoral immune response remains extremely relevant for vector-based medicines. Currently, there is no generally accepted approach to preventing the production of neutralizing antibodies to the injected vector. One option suggests using corticosteroids such as prednisone or methylprednisolone to suppress the activity of the immune system. Other immunosuppressants are also used, including cytostatics such as azathioprine, cyclosporine A, mycophenolate mofetil, and tacrolimus [34].

Gene therapy using AAV vectors is particularly promising for adult patients, but not so much for children and adolescents, whose liver is growing, and the body actively produces hepatocytes, which may reduce the efficacy of such treatment [39]. A 2006 rat study compared the effectiveness of various AAV serovars in the context of creation of vectors. It was shown in vivo that AAV vectors are most effective in correcting *UGT1A1* deficiency. However, large inclusions of fat of indeterminate origin were found in the livers of all the involved animals, raising concerns about possible side effects [40].

The deontological problem associated with gene therapy is the risk of patients developing illusory hopes about the effectiveness of conservative therapy, and consequently neglecting other treatment methods, including PT and liver transplantation.

Liver transplantation

Liver transplantation (LT) is the only definitive treatment option for CNS1 [41, 42]. Currently, there are no well-founded recommendations telling why and, in particular, when a CNS1 patient should undergo LT. It is still unclear at what stage of the disease's progression LT should be considered, and which clinical and laboratory indicators are to be taken as signals the patient should be referred to the transplantologist [43] in cases when liver function is preserved and there are no life-threatening conditions that unequivocally call for LT. At the same time, deterioration of the patient's quality of life due to the daily PT sessions, and loss of the effectiveness of this procedure with age can be valid indications for LT. Development of the gene therapy methods raises new questions about the feasibility of LT. The possibility of recovery without surgery is appealing to the patients and their parents, which translates into a long follow-up period that can have episodic spikes of the bilirubin levels to neurotoxic values. Thus, determining the optimal time for LT is a crucial task: performing it too late can lead to irreversible damage to the brain, while opting for the operation at an early age increases the risk of complications. In addition, LT undoubtedly implies intraoperative and postoperative risks, and requires lifelong immunosuppression. There is a case description covering LT from living related donors to four children with CNS1 aged 2, 8.5, 15 months and 13 years. All children exhibited high levels of unconjugated bilirubin against the background of continuous PT. One patient had neurological disorders as a consequence of bilirubin encephalopathy. After transplantation, the bilirubin levels in all children returned to normal, but the patient with neurological deficits and spastic disorders died 10 months later due to chronic aspiration syndrome. The authors of this case highlight the importance of performing LT before the development of neurological disorders [44]. It is important to start therapy (exchange transfusion/plasmapheresis/PT) at the first signs of bilirubin encephalopathy and consider LT at the early stage to prevent neurological complications. There are other studies that confirm the need for early LT, one of them is a clinical case involving a transplantation to an 18-months-old child with CNS1 performed when the growing level of bilirubin triggered development of kernicterus accompanied by neurological complications in the form of depression syndrome, increased muscle tone, and, subsequently, athetoid motor disorders. The patient received a left lobe of the liver from a deceased donor, and the neurological disorders began to subside after that [45]. Other authors have described cases of LT to three patients with CNS1 aged 7, 12, and 3 years. The seven-year-old child had a mental retardation. The twelve-year-old patient had a more severe brain damage: impaired motor coordination, delayed speech, mental and physical development caused by bilirubin encephalopathy. The three-year-old child did not exhibit any signs of a neurological deficit. All of them needed intensive PT, and none had complications connected therewith. Moreover, the two patients with neurological disorders enjoyed better mental and motor development indicator values after PT. These results confirm the opinion that early LT can be an effective treatment method allowing to prevent irreversible brain damage in patients with the disease in question [46].

Multipotent mesenchymal stromal cells

In the last decade, stem cells have been studied intensively as components of treatment of several metabolic disorders, and CNS1. Multipotent mesenchymal stromal cells (MMSCs) have also been used in CNS1 therapy. Such cells can be safely obtained from the fetal membranes or the remaining placental part of the navel cord after natural childbirth. The current experience of using MMSCs in clinical practice confirms their safety and lack of the need for immunosuppressive therapy. Administered intravenously, these cells have been shown to selectively accumulate in the liver; they can then differentiate into hepatocytes, and participate in liver regeneration [47]. Stem cells derived from bone and adipose tissues can restore liver function by differentiating into hepatocytes, and cells derived from the umbilical cord blood differentiate into cellular structures similar to hepatocytes, which express markers specific to hepatocytes and retain the potential for hepatogenesis required in cell therapy. Cells derived from the placenta also have great potential for multilinear differentiation [48–50]. Administration of MMSCs obtained from human umbilical cord blood directly into the liver of mice has shown a high potential for the restoration of liver tissue and its functions [51, 52]. The data from these studies indicate that cells isolated from the umbilical cord have characteristics similar to those of bone marrow stem cells. In a mice model of damaged liver, MMSCs cells distributed throughout the body 7 days after transplantation, including the liver. Fourteen days after transplantation, the liver of mice saw expression of genes specific to hepatocytes. There is a described case of transplanting MMSCs to a child with CNS1 [53]. With six injections of the cells in the background, the duration of PT has decreased to 2 hours a day within 2 years. The positive effect developed within 4–7 days after administration and persisted for 2–3 months. There were no

side effects or complications registered during and after the transplantation. Thus, intravenous transplantation of MMSCs is an effective treatment CNS1 that eases the need for PT, significantly improves the quality of life of patients, and prolongs the use of their own liver [53].

CONCLUSION

CNS is a serious disease with potentially disabling neurological consequences and a possible lethal outcome. To date, no clear protocol for the management of patients with CNS1 has been developed. Phototherapy is the main method of controlling the level of bilirubin in children with this disease; it is applicable from the first days of life, but the quality of life of the patients receiving PT is low because of the need for continuous sessions. Liver transplantation is a radical CNS1 treatment method that implies postoperative risks and the need for lifelong immunosuppression. Moreover, currently, there is no consensus regarding the optimal timing of LT in CNS cases. Gene therapy's safety and effectiveness in CNS patients is being investigated. Although it remains a promising treatment for this disease, doubts remain about its long-term effect and potential harm.

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