Vol 5 | Issue 46 |2024

# PHYSICIAN CONNECT

Dear Doctor,

Greetings from Micro Labs. We are happy to bring you "Physician Connect" which contains latest and interesting news.

This issue contains:



Should you require any article or, medical information, please feel free to contact us at medicalservices@microlabs.in

Looking forward to your valuable feedback.

Best Regards,

Medical Team, Micro Labs Limited.

# 1. Effect of Anxiety and Depression on Asthma Control Levels Among Asthma patients

**Introduction:**

Asthma is a chronic condition of the lower airways that causes inflammation and hyper-reactivity. Asthma has a complex pathophysiology and caused by environmental, genetic, or epigenetic factors.[1] Multiple research investigations have demonstrated that the prevalence of psychological illnesses was higher among those with chronic medical conditions than in the general population. Patients with asthma have been shown to experience psychological illnesses more often than individuals with other chronic illnesses (Figure 1). The exact risk factors that predispose asthmatic patients to develop anxiety or depression are unknown.[2] The purpose of this study was to determine the prevalence of anxiety and depression in adult asthmatics as well as the relationship between asthma control and these psychological disorders.

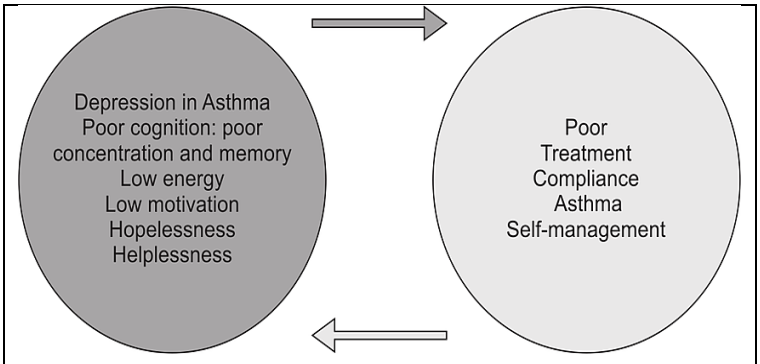


Fig 1. Impact of depression on asthma outcomes.

**Methods:**

This cross-sectional study included 175 asthma patients who had been receiving outpatient follow-up care for more than six months, were over the age of 18, and had been diagnosed with asthma at any severity level. In accordance with GINA guidelines, all patients were receiving pharmacological treatment that included both controller and rescue medications. Patients provided sociodemographic information and self-administered the Hospital Anxiety and Depression Scale (HADS) to assess their depression and anxiety levels. Asthma control was evaluated using the Asthma Control Test (ACT). The study examined the relationship between sociodemographic characteristics and clinical data, specifically depression, anxiety, and asthma control level.

**Results:**

Among 175 asthmatic patients, 60.57% had poor illness control, 8% had anxiety alone, 11.43% had depression alone, and 53.14% had anxiety and depression. Poor asthma control was linked to anxiety and depression (p=0.044). Furthermore, lower levels of education were linked to increased anxiety and depression. This study found that individuals with a high school education or less were more likely to have poorly controlled asthma compared to those with a college or higher educational level. The odds ratio (OR) for people with less than a high school education was 2.5, with a 95% confidence interval (CI) of 1.24 - 5.1. The presence of anxiety and depression in asthma patients was found to be marginally significant (p-value = 0.052).

This suggested that individuals with both depression and anxiety were more likely to experience inadequate asthma control compared to those without either (odds ratio: 2.1; 95% confidence interval: 1.0–4.5) (Table 1).

| Characteristics | Odd ratio | 95% CI | P value |
|---|---|---|---|
| **Level of education** | | | **0.005** |
| Less than high school | 2.5 | 1.24–5.1 | **0.011** |
| High school | 12.3 | 1.5–100.9 | **0.019** |
| **Psychological condition** | | | 0.176 |
| Only anxiety | 1.276 | 0.4–4.4 | 0.701 |
| Only depression | 0.933 | 0.3–2.9 | 0.904 |
| Anxiety and depression | 2.1 | 1.0 –4.5 | **0.052** |

**Note**: Bold P-values are statistically significant ≤ 0.05.

Table 1. Risk factors for poorly controlled asthma (ACT < 20) found using a multivariate logistic regression model.

**Discussion:**

Asthma is a major global health issue that affects people of all ages. This study found 39.43% of patients had well-controlled asthma, which was consistent with earlier findings.[2] A previous study on asthmatic individuals found a 45.2% level of asthma control, with an ACT score <20 indicating poorly managed asthma.[3] In a large cross-sectional study, ESMAA used the ACT questionnaire and 2012 GINA guidelines to assess asthma control among adult patients in the Middle East and North Africa (MENA) found that less than 30% of enrolled patients had well-controlled asthma and they found that the low level of asthma control was related with active smoking, lower education level, or poor commitment to medication use.[4]

**Conclusion:**

The majority of the assessed asthma patients had inadequate management of their condition. The examined sample of individuals with asthma frequently suffered from anxiety and depression, and these psychological illnesses seem to have an impact on the degree of disease

control, raising the possibility that treating these psychological issues may improve asthma control levels.

This study showed a link between anxiety and depression, low education levels, and poor asthma control.

**Reference:**

1. Cevhertas L, Ogulur I, Maurer DJ, Burla D, et al. Advances and recent developments in asthma in 2020. Allergy. 2020 Dec;75(12):3124-3146.
2. Abu Al Karsaneh O, Al Anber A, Al Shboul S et al. Impact of Anxiety and Depression on the Level of Asthma Control Among Jordanian Adults with Asthma. J Asthma Allergy. 2024 May 19;17:463-476.
3. Albataineh E, Al-Zayadneh E, Al-Shagahin H, Al Soloman A, Altarawneh A, Aldmour I. Asthma Control and Its Predictive Factors in Adult Asthma Patients. J Clin Med Res. 2019;11(12):807–817.
4. Tarraf H, Al-Jahdali H, Al Qaseer AH, et al. Asthma control in adults in the Middle East and North Africa: Results from the ESMAA study. Respir Med. 2018;138:64–73.

## 2. Assessment of the reproducibility of the results of Euthyroid Patients with Hashimoto Disease and Persistent Symptoms

**Introduction:**

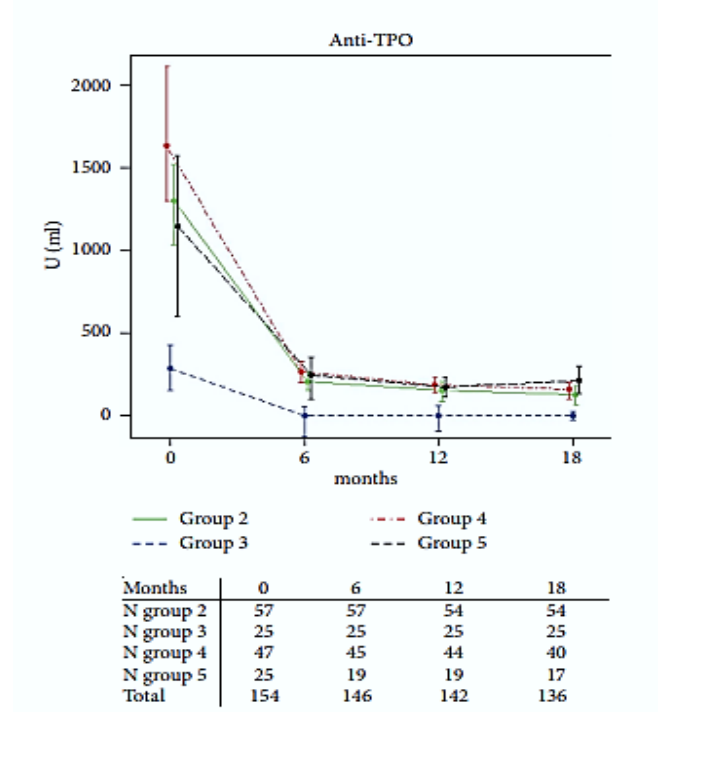
Hashimoto's thyroiditis (HT), the most common autoimmune thyroid disorders (AITD), is the major cause of hypothyroidism in iodine-sufficient areas worldwide. Approximately 20-30% of patients have HT, which was caused by a combination of genetic predisposition and environmental factors. Loss of immune tolerance leads to an autoimmune attack on the thyroid tissue and the emergence of the disease.[1] Despite hormone replacement, certain Hashimoto disease patients may still experience persistent symptoms, suggesting an autoimmune etiology. A randomized trial utilizing patient-reported outcome measures found that complete thyroidectomy was beneficial but had major complication rates.[2] So, this study aimed to replicate the RCT results in an observational study of euthyroid patients with Hashimoto disease, persistent symptoms despite being euthyroid, and a wider range of anti-TPO antibody levels compared to the RCT.

**Methods:**

This observational post randomization study included 154 patients with Hashimoto disease, euthyroid with or without thyroid hormone substitution, and persisting Hashimoto-related symptoms who underwent complete thyroidectomy and were followed for 18 months following surgery. The primary outcome was the General Health (GH) dimensional score from the Short Form-36 Health Survey. Hypocalcemia or postoperative nerve palsy that remained for more than a year were considered long-term surgical side effects.

**Results:**

In this study, 154 (69%) patients underwent total thyroidectomy. Eighteen months following surgery, there was a clinically significant improvement in GH levels, similar to the earlier RCT. Anti-TPO antibody levels decreased significantly following surgery (Figure 1). The multivariate logistic regression model showed that preoperative anti-TPO antibody levels did not affect the outcome in the observational groups. Three (1.9%) of 154 patients developed persistent unilateral recurrent nerve palsy, whereas six (3.9%) developed hypoparathyroidism following surgery.




| Months | 0 | 6 | 12 | 18 |
|---|---|---|---|---|
| N group 2 | 57 | 57 | 54 | 54 |
| N group 3 | 25 | 25 | 25 | 25 |
| N group 4 | 47 | 45 | 44 | 40 |
| N group 5 | 25 | 19 | 19 | 17 |
| Total | 154 | 146 | 142 | 136 |

Figure 1: The effect of complete thyroidectomy on anti-TPO levels. The numbers at risk were listed in the table below the graph.

**Discussion**:

This study showed that thyroidectomy was beneficial for patients with Hashimoto's disease, anti-TPO antibody levels >1000 IU/mL, and persisting symptoms after appropriate thyroid hormone replacement for hypothyroidism. Hashimoto thyroiditis' inflammatory and fibrotic nature can increase the possibility of recurrent nerve palsy and hypoparathyroidism.[2] A prospective observational analysis of 1268 patients with Hashimoto's disease found that 0.9% had permanent nerve palsy and 1.1% had permanent hypoparathyroidism. The findings were comparable to those reported after surgery for benign goiter, with 0.8% nerve palsy and 0.9% hypoparathyroidism.[3] In the present study, there were 7 cases of persistent unilateral nerve palsy (3.1%), resulting in 1.55% per nerve at risk.[2]

**Conclusion**:

For those with Hashimoto's disease who continue to experience symptoms even after being kept euthyroid with or without hormone replacement therapy, a total thyroidectomy may be beneficial and long-lasting. Although there is a high rate of complications associated with the meticulous dissection thought to be necessary, the procedure might be advantageous in some cases. Anti-TPO antibody titers don't seem to be useful in the patient selection process; instead, surgery ought to be done in specialized facilities and as a component of additional, preferentially blinded studies concerning chronic symptoms.

Thyroidectomy can reduce symptoms in euthyroid patients with Hashimoto disease and chronic symptoms.

**Reference**:

1. Ragusa F, Fallahi P, Elia G, Gonnella D, et al. Hashimotos' thyroiditis: Epidemiology, pathogenesis, clinic and therapy. Best Pract Res Clin Endocrinol Metab. 2019 Dec;33(6):101367.
2. Hoff G, Bernklev T, Johnsen L, Reitsma L, et al. Thyroidectomy for Euthyroid Patients with Hashimoto Disease and Persistent Symptoms: An Observational, Postrandomization Study. J Thyroid Res. 2024 Apr 4;2024:5518720.
3. Thomusch O, Sekulla C, Billmann F, Seifert G, Dralle H, Lorenz K; Prospective Evaluation Study of Thyroid Surgery (PETS 2) Study Group. Risk profile analysis and complications after surgery for autoimmune thyroid disease. Br J Surg. 2018 May;105(6):677-685.

## 3. Appropriateness of indications for and dose intensification of statin therapy among Type 2 Diabetic Patients

**Introduction**:

Type 2 Diabetes Mellitus (T2DM) is a common metabolic condition caused by inadequate insulin production by pancreatic β-cells and inability of insulin-sensitive tissues to respond. It is a chronic metabolic condition that causes damage to the heart, vascular system, eyes, kidneys, and nerves.[1] T2DM causes roughly 75% of all atherosclerosis-related events. Diabetes accounts for 65% of all cardiovascular disease and stroke deaths. Lipid-lowering statin treatment was suggested for both primary preventions of atherosclerotic cardiovascular illnesses and secondary prevention in T2DM patients with established cardiovascular disease. There was little information available on the appropriate use of statins for primary and secondary prevention of CVD.[2] So, this study aimed to assess the effectiveness of increasing statin doses for both primary and secondary prevention of CVD in T2DM patients.

**Methods**:

This was a hospital-based cross-sectional study included 405 T2DM patients using a systematic random sampling technique and had follow-up in hospital during the study period. Variables including lifestyle, illness state, and sociodemographic traits were included in the questionnaire. The ASCVD score was also determined using a calculator and an ASCVD risk estimator. A structured questionnaire was used for in-person interviews with all eligible study participants. The data were analysed with SPSS version 26.0.

**Results**:

Of the total 405 individuals, 346 (85.4%) started taking statins for primary or secondary prevention. Statin usage was suitable for 96.2% of patients, with 216 (62.4%) receiving appropriate dose intensification. Atherosclerotic cardiovascular disease (ASCVD) score of ≥7.5% (AOR=0.28; 95% CI: 0.102–0.738, p=0.01), dyslipidemia (AOR=4.48; 95% CI: 1.85–10.84; p=0.001), starting aspirin therapy (AOR=3.7; 95% CI: 1.522–9.144; p=0.004), and an LDL-cholesterol level of 70–189 mg/dL (AOR=0.124; 95% CI: 0.042–0.365; p=0.001) were all associated with the inappropriateness of statin use. Inappropriate statin intensification was associated with DM duration of ≥10 years (AOR=2.51; 95% CI: 1.35-4.66, p=0.004), male gender (AOR=2.04; 95% CI: 1.16-3.58, p=0.013), age ≥65 years (AOR=2.15; 95% CI: 1.23-3.75, p=0.007), and uncontrolled blood pressure (AOR=2.09; 95% CI: 1.07-4.08, p=0.031) (Table 1).

| Variables | | Inappropriate Indication N (%) | Appropriate Indication N (%) | COR (95% CI) | AOR (95% CI) | P-value |
|---|---|---|---|---|---|---|
| Sex | Male | 18 (9.8) | 165 (90.2) | 1.00 | 1.00 | |
| | Female | 36 (16.2) | 186 (83.8) | 1.774 (0.97,3.244) | 1.22 (0.495,3.008) | 0.666 |
| DM duration | ≥10year | 28 (11.7) | 211 (88.3) | 1.00 | 1.00 | |
| | <10year | 26 (15.7) | 140 (84.3) | 1.399 (0.788,2.487) | 0.72 (0.308,1.669) | 0.441 |
| Comorbidity | Yes | 35 (10.8) | 309 (89.8) | 1.00 | 1.00 | |
| | No | 19 (31.14) | 42 (68.8) | 3.994 (2.096,7.611) | 1.38 (0.368,5.166) | 0.634 |
| Hypertension | Yes | 30 (10.6) | 252 (89.4) | 1.00 | 1.00 | |
| | No | 24 (19.5) | 99 (80.5) | 2.036 (1.135,3.655) | 0.35 (0.044,2.776) | 0.319 |
| Dyslipidemia | Yes | 8 (4.5) | 171 (95.5) | 1.00 | 1.00 | |
| | No | 46 (20.4) | 180 (79.6) | 5.462 (2.505,11.909) | 4.48 (1.85,10.839) | **0.001** |
| On antihypertensives | Yes | 28 (10.4) | 241 (89.6) | 1.00 | 1.00 | |
| | No | 26 (19.1) | 110 (80.9) | 2.034 (1.14,3.632) | 2.29 (0.365,14.306) | 0.377 |
| Aspirin | Yes | 13 (6.9%) | 176 (93.1) | 1.00 | 1.00 | |
| | No | 41 (19%) | 175 (81) | 3.172 (1.643,6.125) | 3.73 (1.522,9.144) | **0.004** |
| ASCVD (n=296) | Low risk | 25 (29.5) | 60 (70.5) | 1.00 | 1.00 | |
| | Borderline | 10 (30.3) | 23 (69.7) | 1.043 (0.434,2.508) | 1.01 (0.374,2.724) | 0.985 |
| | Intermediate | 7 (7.8) | 83 (92.2) | 0.202 (0.082,0.499) | 0.28 (0.102,0.738) | **0.01** |
| LDL | <70mg/dL | 14 (20.6) | 54 (79.4) | 1.00 | 1.00 | |
| | 70–189mg/dL | 39 (12.6) | 271 (87.4) | 0.555 (0.282,1.092) | 0.12 (0.042,0.365) | **0.001** |
| | ≥190mg/dL | 1 (11.1) | 8 (88.9) | 0.482 (0.56,4.182) | 1.633 (0.64,41.829) | 0.767 |

**Note**: p-values in bold are statistically significant (<0.05).
**Abbreviations**: ASCVD, atherosclerotic cardiovascular disease; LDL, low density lipoprotein.

Table 1: Predictors of Inappropriate Statin Indication in Type 2 Diabetic Patients

**Discussion:**

The study assessed the appropriateness and intensification of statin treatment in compliance with the 2018 American Diabetes Association (ADA) Standard Medical Care in Diabetes guideline. Assessing ASCVD risk for diabetes patients was critical for modifying treatment and deciding on statin medication for primary prevention.[2] The 2018 Cholesterol Clinical Practice Guidelines recommend utilizing a validated risk prediction tool and measuring ASCVD risk variables to conduct a quantitative 10-year risk assessment.[3] This study analyzed the 10-year ASCVD risk of 296 patients who should take statins for primary prevention to see if statin intensification therapy was necessary. Among those, 29.7% had a significant ASCVD risk (≥20%).

**Conclusion:**

The study showed that the statin indication was optimal, with about two-thirds of patients receiving suitable dose intensifications. To prevent incorrect intensification of statin medication, it's important to monitor patients with long-term diabetes, male gender, advanced age, and uncontrolled blood pressure.

To prevent wrong intensification of statin therapy, it's essential to monitor patients with long-term diabetes, male gender, advanced age, and uncontrolled blood pressure.

**Reference:**

1. Galicia-Garcia U, Benito-Vicente A, Jebari S, Larrea-Sebal A, Siddiqi H, Uribe KB, Ostolaza H, Martín C. Pathophysiology of type 2 diabetes mellitus. International journal of molecular sciences. 2020 Aug 30;21(17):6275.
2. Fisseha PY, Baye AM, Beyene MG, Makonnen E. Evaluation of Statin Indication and Dose Intensification Among Type 2 Diabetic Patients at a Tertiary Hospital. Diabetes Metab Syndr Obes. 2024 Mar 7;17:1157-1169.
3. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2019 Jun 25;73(24):3168-3209.

## 4. Case report on Type II Crigler-Najjar syndrome

**Introduction:**

Crigler-Najjar syndrome (CNS) is a liver metabolic condition caused by mutations in the UGT1A1 gene, which encodes the enzyme responsible for bilirubin conjugation. Severely ill patients may develop jaundice due to high amounts of unconjugated bilirubin and levels above 300 µmol per liter might lead to neurologic damage and death.[1] Type I, which was discovered in 1952 by Crigler and Najjar, is the full lack of UGT1A1 enzyme activity and does not respond to phenobarbital. On the other hand, type II, which was discovered by Arias, is partial loss of UGT1A1 enzyme activity and is responsive to phenobarbital treatment.[2] This case described a 29-year-old male patient presented to the hospital with acute jaundice.

**Case presentation:**

The patient was a 29-year-old male who was taken to the hospital with severe jaundice. His parents claimed that he had icterus and pruritus from birth and had not received any therapy. He was 163 cm tall and 81 kg in weight. All hemolytic anemia measures, including hemoglobin, coagulation function, thyroid function, ceruloplasmin, and immunoglobulin, were within normal limits. The total bilirubin level was 237.8 µmol/L, with unconjugated bilirubin at 228.8 µmol/L. A computed tomography (CT) scan revealed a modest density and normal structure of the liver. The CT index was 50 HU, which indicated fatty liver (Figure 1). A hepatic biopsy revealed bullous steatosis of the hepatic lobule's peri-central veins, bile pigment sedimentation, and mild periportal inflammation, all with normal liver plate structure (Figure 2). There was no consanguinity between the patient and his parents. To confirm the diagnosis of type II CNS, blood genomic DNA from both the patient and his parents was collected and sequenced. The genetic tests revealed two possible homozygous harmful variants. One mutation was the c.1456 T > G p.Y486D homozygous mutation. Y486D was found on exon 5, and it converts 1,456 thymine (T) to guanine (G) and 486 tyrosine (Tyr) to aspartic acid (Asp). His parents were heterozygous carriers of the c.1456 T > G p. Y486D gene. The second mutation was the c.211G > A p. G71R homozygous mutation. G71R was noted in exon 1, where it converts 211 guanine (G) to adenine (A) and changes residue 71 from glycine (Gly) to arginine (Arg). His father was a c.211G > A p. G71R homozygous carrier with no symptoms, whereas his mother was a heterozygous carrier. The patient then was diagnosed with type II CNS. Since then, he has been taking phenobarbital (180 mg/day) to lower his bilirubin levels and prevent jaundice. After that, his total bilirubin levels ranged between 100 and 200 µmol/L for 6 months, with no significant icterus or pruritus as side effects.

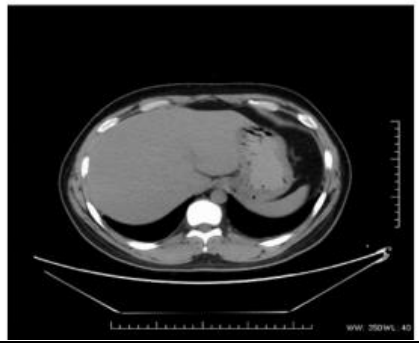


Figure 1: CT scan of the patient. The liver has a low density and regular shape (CT index of 50 U).

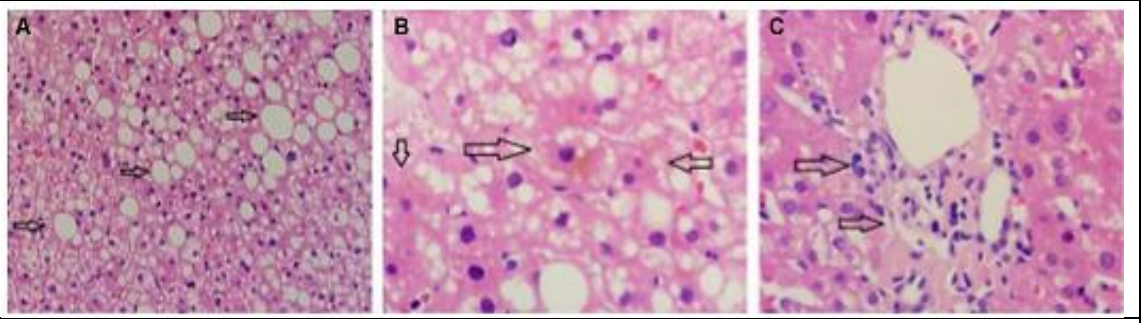



Figure 2: Pathology of liver biopsy. (A) A normal hepatic plate structure with bullous steatosis of the peri-central veins of the hepatic lobule (arrow), (B) Bile pigment sediment (as indicated by the arrow), (C) Mild periportal irritation.

**Discussion:**

This case report described a rare case of type II CNS. Routine genome sequencing was used to diagnose type II CNS. Phenobarbital was the most effective medicine for CNS disorders, particularly type II CNS, as it induces UGT1A1 activity. [2] A previous study showed that, Phenobarbital, a barbiturate that lowers blood bilirubin levels, was used to treat Crigler Najjar syndrome type II and Gilbert syndrome.[3]

**Conclusion:**

Phototherapy therapy and medication therapy, such as phenobarbital, are beneficial for type II CNS, and the prognosis can be favorable. On the other hand, type I CNS patients may eventually require a liver transplant.

Gene sequencing can be utilized to diagnose Type II Crigler-Najjar syndrome (CNS), which can then be treated with phenobarbital.

**References:**

1. D'antiga L, Beuers U, Ronzitti G, Brunetti-Pierri N, Baumann U, Di Giorgio A, Aronson S, Hubert A, Romano R, Junge N, Bosma P. Gene therapy in patients with the Crigler–Najjar syndrome. New England Journal of Medicine. 2023 Aug 17;389(7):620-31.
2. He T, Geng X, Zhu L, Lin X, Wang L. Type II Crigler-Najjar syndrome: a case report and literature review. Front Med (Lausanne). 2024 May 9;11:1354514.

3. Tcaciuc E, Podurean M, Tcaciuc A. Management of Crigler-Najjar syndrome. Med Pharm Rep. 2021 Aug;94(Suppl_1):S64-S67.