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# Acute intermittent porphyria: A case report with an unlisted *HMBS* gene variant (c.345–2A>C)

Julien Lerusse [a,*], Dominique Dive [b], François Charles Wang [c]

[a] Hôpitaux Univeristaires de Genève, Department of Clinical Neuroscience, Geneve, Rue Gabrielle-Perret-Gentil 4, 1205 Genève, Swiss
[b] Centre Hospitalier Universitaire de Liège, Department of Neurology, Sart Tilman B35, 4000 Liège, Belgium
[c] Centre Hospitalier Universitaire de Liège, MPR Department, Sart Tilman B35, 4000 Liège, Belgium

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ABSTRACT

We report a case of acute intermittent porphyria in a 19-year-old patient, linked to an unlisted variant of the gene encoding hydroxymethylbilane synthase c.345–2A>C. Given the very low prevalence of porphyria in the general population, diagnosis is rarely made initially and may mainly mimic Guillain-Barré syndrome. Considering this, we provide an overview addressing various ways the disease manifests, paraclinical investigations, pathophysiology, and available therapeutic options. Specifically, human heme therapy in the case of acute crises is nearly unanimous in the literature. However, there is no consensus on the management between crises if the current first line choice treatment, namely givosiran, is not accessible. We report the clinical follow-up proposed for this patient.

## 1. Report of case

The patient was a 19-year-old female with a history of psychomotor development delay in the context of a meningeal hemorrhage with seizures in early childhood following a shaken baby syndrome. She was treated for epilepsy with valproic acid (Depakene), institutionalized, and able to walk without technical assistance. There was no relevant family history.

The patient was initially hospitalized for an evaluation of worsening behavioral disorders with deterioration in general condition, nausea, and vomiting. She experienced acute respiratory failure during this hospitalization, requiring intensive care, tracheostomy with invasive ventilation, and gastrostomy. At the same time, she developed a rapidly progressive flaccid tetraplegia with osteotendinous areflexia, peripheral facial diplegia, and dysautonomic symptoms (tachycardia, erythro-acrocyanosis). Electrodiagnostic (EDX) showed nearly absence of sensory and motor responses in all four limbs. The only evocable motor response came from the right deltoid muscle with a collapsed amplitude of 0.3 mV (Table 1). Fibrillations and positive sharp waves were abundantly recorded in the right deltoid and right quadriceps muscles. Given this clinical and electrophysiological presentation, a diagnosis of Guillain-Barré syndrome, axonal form (Acute Motor and Sensory Axonal Neuropathy or AMSAN), was made. The immediate response to immunoglobulin therapy (2 g $Kg^{-1}$) was poor.

After three months, the patient's clinical condition partially improved, allowing for ventilator weaning and discharge from the intensive care unit. Motor recovery included gradual shoulder abduction and partial elbow flexion. She was then transferred to neurorehabilitation. Three months later, during this stay, in the space of about ten days, the situation significantly deteriorated. This relapse initially manifested with abdominal pain, particularly intense in the right iliac fossa, with a certain degree of tenderness on palpation, raising concerns about acute appendicitis. At the same time, the patient was tachycardic and presented with severe constipation, followed by persistent diarrheal stools. The patient became mute and apathetic, then experienced a loss of consciousness with a 30-second episode of clonic movements. When she emerged from unconsciousness, she went through a phase of depression with a feeling of abandonment by her parents. Her thymic state further deteriorated, and she experienced hallucinations. The situation then worsened on the motor side, with a new episode of flaccid tetraplegia. The extremities were erythro-cyanotic. The lumbar puncture revealed albuminocytologic

*List of abbreviations:* ACMG, American College of Medical Genetics and Genomics; ALA, Delta-aminolevulinic acid; AMP, Association for molecular pathology; AMSAN, Acute motor and sensory axonal neuropathy; ATPase, Adenosine triphosphatase; EDX, Electrodiagnostic; GABA, Gamma-aminobutyric acid; HMBS, Hydroxymethylbilane synthase; MRI, Magnetic resonance imaging; PBG, Porphobilinogen; RNA, Ribonucleic acid; XLT, X-linked thrombocytopenia.

* Corresponding author at: Lerusse Julien, Département des Neurosciences Cliniques, Service de Neurologie, Rue Gabrielle-Perret-Gentil 4, 1205 Genève, Suisse
*E-mail address:* Julien.Lerusse@hug.ch (J. Lerusse).

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dissociation with a protein level of 1400 mg/l. This motor relapse, along with abdominal pain, neurobehavioral disturbances, and dysautonomia, prompted an expanded diagnostic exploration. Vasculitis, heavy metal poisoning, and infectious causes (hepatitis B and C, human immunodeficiency virus, cytomegalovirus, Epstein-Barr virus, syphilis, *borrelia burgdorferi*, and *campylobacter jejuni*) were ruled out.

Around eight months from the first flaccid tetraplegia episode, the diagnosis of acute intermittent porphyria was considered based on an increase in porphyrin precursors, delta-aminolevulinic acid (ALA) and porphobilinogen (PBG), in the urine (Table 2). Hydroxymethylbilane synthase (HMBS) activity was measured twice in red blood cells, with results at the lower limit of normal. Ultimately, it was the molecular biology analysis that revealed a heterozygous variant of the *HMBS* gene c.345–2A>C (which destroys the splice acceptor site of intron 7), leading to the diagnosis of acute intermittent porphyria caused by a non-erythroid variant of the disease. The pathogenic nature of this variant had already been highly suspected in the literature [1]. The patient had no prior history of porphyria. Unfortunately, the patient's two biological parents, as well as her two half-brothers and half-sister, never attended the genetic consultations that were offered to them and therefore could not be genetically tested.

Given that valproic acid (Depakene) is highly porphyrinogenic, it was discontinued as soon as porphyria was suspected. The patient then received other antiepileptics for different therapeutic purposes: gabapentin (Neurontin) for her neuropathic pain and lamotrigine (Lamictal) for her mood disorders. The patient was infused with a hypertonic glucose solution and treated with human heme. We opted for a treatment with human heme over two years, with six courses (over four days) per year. This treatment was intended to be both therapeutic (reducing the amounts of ALA and PBG to limit their toxic effects) and prophylactic to prevent further attacks. After this two-year period, human heme was only administered when we observed a significant increase in urinary porphyrin precursors. In the span of 7 months, the urinary PBG and ALA decreased significantly (Table 2). The clinical progress was also favorable. After approximately a year of this treatment combined with rehabilitation, the patient could perform transfers independently, had meals autonomously, performed personal hygiene, dressed herself, and walked with a double support and the use of orthopedic devices. Analytically, there was still motor deficit and atrophy predominantly in the distal parts of all four limbs, severe sensory disturbances predominantly in the lower limbs, abolition of osteotendinous reflexes in the lower limbs, and a significant reduction in the upper limbs. Tracheostomy and gastrostomy were removed. Behavioral issues returned to their baseline state before acute porphyria episodes.

The EDX data also showed improvement (Table 1). After one year of treatment by human heme, motor amplitudes increased, electromyographic traces reappeared in both quadriceps muscles in the form of numerous polyphasic potentials, indicative of ongoing reinnervation processes. On the sensory side, responses continued to be absent.

Two years after the onset of symptoms, an "involuntary" attempt at therapeutic withdrawal, as the patient was admitted to another hospital for an issue unrelated to porphyria, resulted in a neurologic relapse, like the previous one in clinical and electrophysiological terms. Monitoring of urinary ALA and PBG (monthly), regular neurological clinical follow-up, and electrophysiological assessments, initially performed twice a year, are then implemented. This was done to optimize the management of human heme therapy due to the patient's unreliable medical history, particularly regarding digestive symptoms.

**Table 2**
measurements of porphyria precursors in the urine.

| | PBG µmol/mmol | ALA µmol/mmol | PBG mg $g^{-1}$ | ALA mg $g^{-1}$ |
|---|---|---|---|---|
| At the time of suspicion of a porphyria diagnosis | NA | 36.4 | NA | 42.2 |
| After second treatment by human heme (2 months later) | 79.0 | 23.9 | 157.9 | 27.7 |
| After sixth treatment by human heme (9 months later) | 26.0 | 9.8 | 51.0 | 11.37 |

PBG = urinary porphobilinogen normalized by urinary creatinine; ALA = delta-aminolevulinic acid normalized by urinary creatinine; the PBG upper normal limit = 0.8 µmol/mmol, the ALA upper normal limit = 5.5 µmol/mmol; NA = not available.

## 2. Discussion

Initially, the clinical presentation strongly suggested an axonal form of Guillain-Barré syndrome, specifically AMSAN. However, due to the lack of a favorable response to intravenous immunoglobins, the presence of abdominal pain, significant neurobehavioral disturbances, autonomic dysfunction, and an increase in ALA and PBG in the urine (Table 2), the diagnosis of acute intermittent porphyria was considered. As a result, the patient was successfully, this time, treated with human heme. Molecular biology analysis revealed an unlisted heterozygous variant of the *HMBS* gene c.345–2A>C. According to the classification using the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) guidelines, the variant identified in this patient was considered « likely pathogenic »: 1) This variant affects one of the canonical splice sites which could result in exon 7 skipping, preserving the reading frame but altering a crucial region for protein function; 2) This variant has not been reported in the Genome Aggregation Database 4.0; 3) The variant has been identified in

**Table 1**
Eletrodiagnostic data at the onset of the first episode of acute tetraplegia [1] and after one year of treatment with human heme [2].

| Compound muscle action potential | Amplitude (mV) | | LN | DL (ms) | | LN | Duration (ms) | | LN |
|---|---|---|---|---|---|---|---|---|---|
| | **1** | 2 | | **1** | **2** | | **1** | **2** | |
| **Right median** (wrist – APB) | NR | 0.3 | > 4.4 | | 7.2 | < 4.5 | | 13.0 | < 8.0 |
| **Left median** (wrist – APB) | | 0.5 | > 4.4 | | 7.5 | < 4.5 | | 14.3 | < 8.0 |
| **Right ulnar** (wrist – ADM) | | 3.1 | > 6.8 | | 4.8 | < 3.5 | | 11.2 | < 9.0 |
| **Left ulnar** (wrist – ADM) | | 2.4 | > 6.8 | | 4.5 | < 3.5 | | 12.0 | < 9.0 |
| **Right fibular** (ankle – EDB) | | NR | > 2.3 | | | | | | |
| (PF- TA) | NR | | > 4.5 | | | | | | |
| **Right tibial** (ankle – AHB) | NR | | > 6.2 | | | | | | |
| **Right axillaris** (Erb – Deltoid) | 0.29 | 11.0 | > 10.8 | 5.9 | 5.7 | < 5.0 | | | |
| **Left axillaris** (Erb – Deltoid) | NR | | > 10.8 | | | | | | |
| Sensory nerve action potential | Amplitude (µV) | LN | | | | | | | |
| | 1 | 2 | | | | | | | |
| **Left radial** (forearm – wrist) | NR | NR | > 25.0 | | | | | | |

DL = distal latency; PF = popliteal fossea; APB = *abductor pollicis brevis* muscle; ADM = *abductor digiti minimi* muscle; EDB = *extensor digitorum brevis* muscle; AHB = *abductor hallucis brevis* muscle; TA = *tibialis anterior* muscle; NR = no response; LN = limits of normality established in our laboratory.

the literature in another patient with acute intermittent porphyria and has been classified as likely pathogenic [1]; 4) Biochemical studies support a diagnosis of acute intermittent porphyria. Nevertheless, a ribonucleic acid (RNA) analysis would be necessary to prove the pathogenicity of the c.345–2A > C variant.

Porphyria is a metabolic disease resulting from a deficiency in one of the eight enzymatic steps in heme synthesis (Fig. 1) [2]. In the present case, corresponding to acute intermittent porphyria, the deficiency involves hepatic *HMBS* gene, leading to the accumulation of ALA and PBG, with the consequence of primarily affecting the nervous system [3]. Not all porphyrias are due to decreases in activities of enzymes. X-linked thrombocytopenia (XLP) is due to gain-of-function mutations in *ALAS2* gene [4].

Acute intermittent porphyria is autosomal dominant. The incidence of symptomatic acute porphyria in the general population is estimated at 0.13 per million per year in Europe, with a prevalence of 5.4 per million per year. Penetrance is incomplete, and the majority of mutation carriers will never develop symptoms [5].

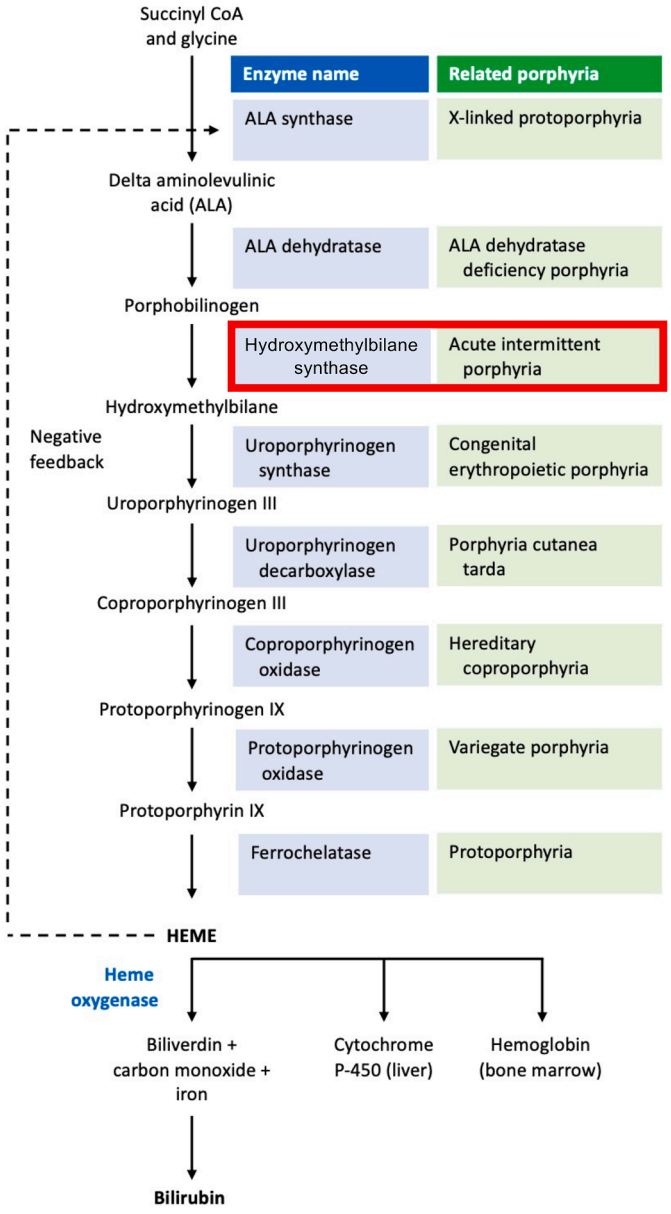


**Fig. 1.** The Pathway of Heme Synthesis, Showing Pathway Intermediates and End-Product Regulation by Heme. The eight steps of heme synthesis (left column) are shown with the enzyme (middle column) that catalyzes each step. From: Bessis D, Marque M, Dereure O. Porphyries cutanées. EMC (Elsevier Masson SAS, Paris), Dermatologie, 98–240-A-10, 2007[14].

The most affected patients are generally young women between 20 and 40 years old. Complaints are varied and nonspecific, including fatigue, concentration difficulties, mood irritability, abdominal pain, and neurological disorders [2]. Regarding the case reported in this article, it was especially noteworthy since the patient did not initially present with clear abdominal symptoms. Abdominal pain is often prominent, but the differential diagnosis of acute abdomen rarely includes porphyria due to unfamiliarity with the condition. Neurological manifestations of acute intermittent porphyria include alterations in consciousness, neurovascular involvement, polyneuropathies with axonal degeneration, behavioral disorders, and epileptic seizures. Reversible posterior encephalopathy and reversible cerebral vasoconstriction syndrome have also been described [6,7]. It is not typical to observe, as in our observation, an increase in protein concentration in the cerebrospinal fluid during an acute porphyria attack. Nevertheless, the accumulation of toxic metabolites (ALA and PBG) is likely to induce oxidative stress, which may lead to disruption of the blood-brain barrier.

The pathophysiology remains debated. Some authors link neuronal dysfunction to an intraneural heme deficiency [8,9], while others invoke the direct toxicity of ALA and other overproduced metabolites such as PBG [8]. As the structure of ALA is close to gamma-aminobutyric acid (GABA), the hypothesis of competition with GABAergic pathways could be considered [9,10].

Regarding the peripheral nervous system, the incidence of affected patients varies from 10 – 40 % [2]. Here too, the exact underlying mechanisms of neuropathy remain uncertain, but the toxic role of heme precursor accumulation leading to $Na^{+}/K^{+}$ adenosine triphosphatase (ATPase) pump dysfunction could be one explanation leading to axonal degeneration [11]. During human heme treatment, the improvement in the patient's neuropathy is not a direct effect. Human heme does not reverse the neuropathy but acts by terminating the attack to allow the nerves to slowly regrow. Our patient's respiratory failure was certainly secondary to peripheral nervous system involvement. Additional symptoms such as swallowing difficulties, incontinence, or urinary retention are described in the literature [12].

Porphyric crises are notably triggered by combined oral contraceptive use and the menstrual cycle at the peak of the progestational phase. Progesterone and low glucose leading to an up-regulation of hepatic ALA synthase-1, can contribute to these crises. Reduced carbohydrate intake is also an indirect activator of this enzyme and may precipitate crises. Other direct or indirect activators, such as alcohol and numerous drugs inducing cytochrome P450, should be monitored carefully [13]. In the case presented in this article, valproic acid (Depakene) certainly played a decisive role in triggering the first crisis. Before introducing any medication, it is essential to check for contraindications, and the website https://www.porphyrie.net/medicaments/ is regularly updated for reference.

Biologically, routine tests may show nonspecific anomalies. Hyponatremia is frequently observed, possibly due to inappropriate secretion of antidiuretic hormone (from hypothalamic supraoptic nucleus involvement) but also potentially related to vomiting, diarrhea, and renal sodium losses. Liver function test alterations may also be present [14]. For years, the diagnosis or detection of a crisis relied on 24-hour urine collection, leading to delays in initiating treatment. Currently, the development of rapid and cost-effective spot urine tests allows for a quick assessment of ALA and PBG concentrations. During a crisis, the levels found are 20 to 50 times normal. Blood tests are useful for crisis follow-up. Other quantitative tests may aid in diagnosing various forms of porphyria, but genetic sequencing is preferred [15].

From a therapeutic perspective, there is compelling evidence to recommend the use of intravenous heme, especially in severe crises, as first-line treatment. As an intermediate therapy, glucose infusion may be used as a supplement or in cases of mild crises. Prophylactic heme treatment is not recommended due to insufficient evidence, but in

practice, it is often used in many countries to prevent recurrent crises [16]. In the present case, in the medium term, the plan was to perform urinary PBG and ALA measurements multiple times during symptom-free periods to gain a better understanding of the baseline continuous expression of these metabolites, and to reserve heme treatment only for actual porphyria crises accompanied by a significant increase in urinary concentrations of these metabolites. However, possible side effects of chronic infusions include iron overload, which may promote chronic inflammatory liver conditions with fibrosis. Studies on this aspect are contradictory. Other possible side effects are headaches, phlebitis, catheter-related complications, local pain, and skin reactions. There is currently limited information on the recommended administration protocol. In the case of chronic heme administration, quantitative measurement of hepatic iron by T2-weighted magnetic resonance imaging (MRI) is recommended and appears more reliable than ferritin levels. A new therapy, givosiran, was introduced to the European market in March 2020. This monthly-administered medication is based on small interfering RNA (siRNA) technology, blocking the transcription of certain mRNA. In this case, it leads to partial inhibition of the synthesis of 5-ALA (the first enzymatic step in heme synthesis; Fig. 1), reducing ALA and PBG concentrations during acute crises. This medication has resulted in a decreased recurrence of crises, reduced heme use, and a significant improvement in patients' quality of life and daily pain [17].

In the present observation, givosiran would have been an appropriate treatment but was not accessible. Indeed, this treatment was not yet available on the market at the time of diagnosis. After it became available, the patient no longer experienced any events suggesting a new porphyria attack that would have required its introduction. This treatment is reserved for severe cases, as some serious adverse events have been reported, possibly explained by elevated homocysteine levels (cerebral venous thrombosis, pulmonary embolism, pancreatitis). Emerging therapies aiming to spare human heme treatment appear promising to improve the prognosis of this condition, which carries significant morbidity and mortality related to the disease or potential complications from long-term treatments [18].

## CRediT authorship contribution statement

**Julien Lerusse:** Writing – original draft, Conceptualization. **Dominique Dive:** Validation, Investigation. **François Charles Wang:** Writing – review & editing, Validation, Supervision, Investigation.

## Declaration of competing interest

No conflict of interest to be reported.

## References

[1] S. Dragneva, M. Szyszka-Niagolov, A. Ivanova, L. Mateva, R. Izumi, Y. Aoki, et al., Seven novel mutations in bulgarian patients with acute hepatic porphyrias (AHP), JIMD. Rep. 16 (2014) 57-64.
[2] J.W. Albers, J.K. Fink, Porphyric neuropathy, Muscle Nerve 30 (2004) 410–422.
[3] U. Gross, S. Sassa, K. Jacob, J.C. Deybach, Y. Nordmann, M. Frank, et al., 5-Aminolevulinic acid dehydratase deficiency porphyria: a twenty-year clinical and biochemical follow-up, Clin. Chem. 44 (9) (1998) 1892-6.
[4] T. Wang, Y. Wang, Q. Dong, C. Xu, X. Zhou, Y. Ouyang, et al., X-linked dominant protoporphyria in a Chinese pedigree reveals a four-based deletion of ALAS2, Ann. Transl. Med. 8 (2020) 344.
[5] Y. Nordmann, H. Puy, V. Da Silva, S. Simonin, A.M. Robreau, C. Bonaiti, et al., Acute intermittent porphyria: prevalence of mutations in the porphobilinogen deaminase gene in blood donors in France, J. Intern. Med. 242 (3) (1997) 213-7.
[6] M. Oliveira Santos, M Leal Rato, Neurology of the acute hepatic porphyrias, J. Neurol. Sci. 428 (2021) 117605.
[7] K. Wylie, F.D. Testai, Neurological manifestations of acute porphyrias, Curr Neurol Neurosci Rep. juill 22 (7) (2022) 355-62.
[8] D.M. Bissell, K.E. Anderson, H.L Bonkovsky, Porphyria. Longo DL, éditeur, N. Engl. J. Med. 377 (9) (2017) 862-72.
[9] J.A. Tracy, P.J.B. Dyck, Porphyria and its neurologic manifestations, Handb. Clin. Neurol. 120 (2014) 839-49.
[10] M.J.W. Brennan, R.C. Cantrill, δ-Aminolaevulinic acid is a potent agonist for GABA autoreceptors, Nature 280 (5722) (1979) 514-5.
[11] C.S.Y. Lin, A.V. Krishnan, M.J. Lee, A.S. Zagami, H.L. You, C.C. Yang, et al., Nerve function and dysfunction in acute intermittent porphyria, Brain 131 (9) (2008) 2510-9.
[12] P.E. Stein, M.N. Badminton, D.C. Rees, Update review of the acute porphyrias, Br. J. Haematol. 176 (4) (2017) 527-38.
[13] V.R.S. Júnior, V.M.V. Lemos, I.M.L. Feitosa, R. Florencio, C.W.B. Correia, L.B. C. Fontes, et al., Effect of menstrual cycle on acute intermittent porphyria, Child Neurol. Open. 4 (2017) 2329048X1773617.
[14] D. Bessis, M. Marque, O. Dereure, Porphyries cutanées, EMC - Dermatologie 2 (4) (2007) 1-12.
[15] E. Di Pierro, M. De Canio, R. Mercadante, M. Savino, F. Granata, D. Tavazzi, et al., Laboratory diagnosis of porphyria, Diagnostics. (Basel) 11 (8) (2021) 1343.
[16] H.C. Kuo, C.N. Lin, Y.F Tang, Prophylactic heme arginate infusion for acute intermittent porphyria, Front. Pharmacol. 12 (2021) 712305.
[17] A. Ricci, P Ventura, Givosiran for the treatment of acute hepatic porphyria, Expert. Rev. Clin. Pharmacol. 15 (2022) 383–393.
[18] P.E. Petrides, Therapy follows diagnosis: Old and new approaches for the treatment of acute porphyrias, what we know and what we should know, Diagnostics. (Basel) 12 (7) (2022) 1618.