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Research Article

Hereditary Tyrosinaemia Type 1 in Moroccan Children: 18-Year Clinical and Epidemiological Analysis

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Abstract

Background: Hereditary tyrosinaemia type 1 (HT1) is a rare autosomal recessive disorder with variable manifestations. This study aimed to describe clinical and biochemical features of HT1 in Moroccan children.

Methods: This retrospective study included children diagnosed with HT1 and followed at Mohammed V Military Teaching Hospital, Rabat, Morocco, between January 2007 and December 2024. Data were collected using standardised forms covering clinical, biochemical, therapeutic and outcome parameters. Diagnosis was confirmed by elevated succinylacetone.

Results: Ten patients from nine families were included (six females, four males). Consanguinity was present in all cases (first-degree 70%, second-degree 30%). Seven patients (70%) had the acute form and three (30%) the chronic form. Mean age at diagnosis was 8.3 months for acute cases and 62 months for chronic cases. Common presenting signs were abdominal distension (50%) and hepatomegaly (30%). All patients developed hepatic insufficiency; hepatomegaly and growth failure occurred in 90%. Nine patients (90%) received nitisinone. Outcomes were favourable in 70%, while 20% died from hepatic failure.

Conclusion: This study represents the largest paediatric HT1 cohort from Morocco, highlighting the role of consanguinity and delayed diagnosis. Early nitisinone therapy improved outcomes, underscoring the need for diagnostic awareness and newborn screening.

Keywords: *Tyrosinemias; Nitisinone; Succinylacetone; Children; Metabolism; Pediatrics*

Abbreviations

HT1: Hereditary Tyrosinaemia Type 1; NTBC: Nitisinone; MENA: Middle East and North Africa; SA: Succinylacetone

Introduction

Hereditary tyrosinaemia type 1 (HT1) is a rare autosomal recessive disorder caused by fumarylacetoacetate hydrolase deficiency, leading to accumulation of toxic metabolites, particularly succinylacetone. This results in progressive hepatic dysfunction, renal impairment, neurological crises, and increased hepatocellular carcinoma risk if untreated [1]. Clinical presentation ranges from acute liver failure in infants to chronic hepatorenal involvement and hypophosphataemic rickets in older children [2].

Since the introduction of nitisinone (NTBC), HT1 prognosis has improved dramatically through prevention of toxic metabolite formation [1]. Early treatment initiation, particularly via newborn screening, significantly improves survival and neurocognitive outcomes [3].

However, treatment access remains heterogeneous globally, with late diagnoses contributing to morbidity in resource-limited settings [4].

The Middle East and North Africa (MENA) region faces unique challenges due to high consanguinity rates (often >25%) and limited newborn screening programmes [4,5]. Limited data exist on HT1 in North African populations, where specialised metabolic services remain concentrated in urban centres.

Aim of the Study

This study aimed to describe the epidemiological, clinical, biochemical, and radiological characteristics of HT1 in Moroccan children, analyse treatment responses, and compare findings with international cohorts to highlight diagnostic and therapeutic challenges relevant to similar resource-limited settings.

Materials and Methods

This retrospective, descriptive, and analytical study was conducted at the Paediatric Department of Mohammed V Military Teaching Hospital (HMIMV), Rabat, Morocco. The study period spanned 18 years, from January 2007 to December 2024.

Study population

All children diagnosed with HT1 and followed at the paediatric department during the study period were included. Patients were identified through hospital records and metabolic disease databases.

Inclusion criteria: Children followed at the paediatric department of HMIMV Rabat for any of the three clinical forms of HT1 (acute, subacute, or chronic), with diagnostic confirmation by elevated succinylacetone (SA) in urine and/or blood.

Exclusion criteria: Medical records with insufficient clinical or laboratory data, and cases where the diagnosis of HT1 was not formally confirmed by biochemical testing.

Diagnostic criteria

HT1 diagnosis was confirmed by elevated succinylacetone levels measured using liquid chromatography-tandem mass spectrometry (LC-MS/MS). Diagnostic thresholds were defined as succinylacetone levels >20 µmol/L in urine or > 2 µmol/L in blood, representing values significantly above the normal reference range (< 2 µmol/L in urine, < 0.5 µmol/L in blood). Laboratory analyses were performed using standardized protocols at the National Reference Laboratory for Inherited Metabolic Disorders, Rabat, Morocco.

Data collection

A standardised data collection form was developed for each patient, enabling analysis of epidemiological, clinical, laboratory, therapeutic, and evolutionary parameters from archived medical records. Data extraction was performed by two investigators, with 20% of records reviewed independently to ensure accuracy and consistency.

For each patient, the following data were collected:

- Epidemiological data: Year of diagnosis, geographic origin, sex, age at admission, medical coverage, socioeconomic status.
- Personal and family history: Similar cases, consanguinity.
- Clinical data: Chief complaint, age at symptom onset, delay between symptom onset and diagnosis, clinical manifestations.
- Laboratory data: Blood tests (hepatic function, coagulation profile, phosphocalcic metabolism, alpha-foetoprotein, complete blood count, ferritin), urinalysis, amino acid chromatography.

- Radiological findings: Abdominal ultrasound, CT and MRI scans, standard hand X-rays.
- Diagnostic confirmation: Succinylacetone levels in blood and/or urine.
- Clinical form: Acute, subacute, or chronic.
- Therapeutic data: Symptomatic treatment, NTBC therapy, tyrosine- and phenylalanine-restricted diet.
- Evolutionary data: Clinical and biochemical responses, complications, outcomes.

Treatment protocol

NTBC therapy was administered using nitisinone (Orfadin®, Swedish Orphan Biovitrum AB, Stockholm, Sweden) at an initial dose of 1 - 2 mg/kg/day, divided into two doses, with subsequent dose adjustments based on clinical response and biochemical markers. All patients receiving NTBC were placed on a tyrosine- and phenylalanine-restricted diet under the supervision of a metabolic nutritionist. Laboratory monitoring included plasma tyrosine levels (target range 200 - 400 µmol/L), liver function tests, and alpha-fetoprotein levels. Temperature measurements were recorded in degrees Celsius throughout the study period.

Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki and local institutional guidelines. The study protocol was approved by the Ethics Committee of Mohammed V Military Teaching Hospital, Rabat, Morocco. Patient anonymity was maintained throughout data collection and analysis, and informed consent requirements were waived due to the retrospective nature of the study.

Statistical analysis

Given the small sample size (n=10), this study employed purely descriptive analysis without inferential statistics. Categorical variables were expressed as frequencies and percentages, whilst continuous variables were presented as individual values, ranges, means, and medians as appropriate.

The diagnostic delay was calculated as the time interval between symptom onset and confirmed diagnosis. Treatment response was defined as clinical improvement with normalisation or significant reduction in liver enzymes and alpha-fetoprotein levels within 6 months of NTBC initiation. Patient outcomes were described individually and summarized descriptively.

Data calculations were performed using standard spreadsheet software, with all values verified through manual calculation. Missing data points were reported as such, with the extent of missing information specified for each variable.

Results

Ten patients from nine unrelated families were diagnosed with HT1 during the 18-year study period. Baseline demographic and clinical features are presented below. The cohort included six females and four males (female-to-male ratio 3:2). All patients were of Moroccan origin.

Demographics and family history

Sixty percent belonged to middle socioeconomic class. Healthcare coverage was provided for nine patients (90%), whilst one patient (10%) had no insurance coverage.

Parental consanguinity was present in every case, with first-degree consanguinity in 70% (7/10) and second-degree consanguinity in 30% (3/10). Two affected siblings were identified within the cohort (patients 2 and 9). Three unexplained familial deaths were reported, suggesting possible undiagnosed cases.

Clinical presentation

Seven patients (70%) presented with the acute form, whilst three (30%) presented with the chronic form. Mean age at diagnosis was 8.3 months for acute presentation and 62 months for chronic presentation. Median age of symptom onset was 3 months in acute cases and 32 months in chronic cases.

Mean diagnostic delay differed significantly: 4.6 months (range: 2-10 months) for acute cases versus 30 months (range: 12-56 months) for chronic cases. The longest diagnostic delay of 56 months occurred in patient 8, who presented with neurological manifestations initially misattributed to other causes.

The most common presenting complaints were abdominal distension in five patients (50%) and hepatomegaly in three patients (30%). Two patients (20%) were admitted primarily for growth retardation.

Clinical findings at diagnosis

At diagnosis, all patients exhibited hepatic insufficiency with prothrombin time <70%. As shown in figure 1, the most common clinical findings included hepatomegaly and growth failure, each affecting the majority of patients, followed by splenomegaly, pallor, abdominal distension, anorexia, and rickets. Haemorrhagic syndrome was present in 30% (3/10), and psychomotor delay in 20% (2/10).

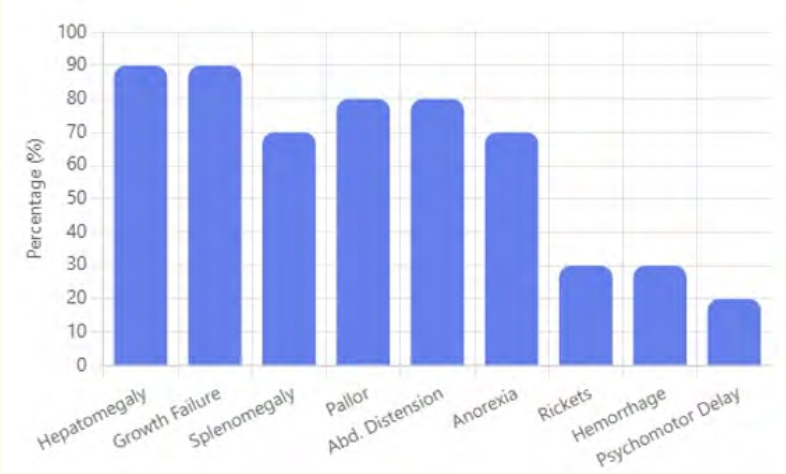

Figure 1: *Clinical signs at diagnosis.*

Laboratory findings

All patients demonstrated liver dysfunction with impaired coagulation profiles and elevated transaminases. Cholestasis and cytolysis were present in 100%, with decreased prothrombin time in all patients and prolonged activated partial thromboplastin time in 80%. Factor V was decreased in 40% and hypoalbuminaemia was present in 30%.

As detailed in figure 2, the key diagnostic markers showed characteristic patterns, with alpha-foetoprotein (AFP) elevation being nearly universal. Normochromic normocytic anaemia and hypophosphataemia were frequently observed. Hypoglycaemia was documented in 40% (4/10).

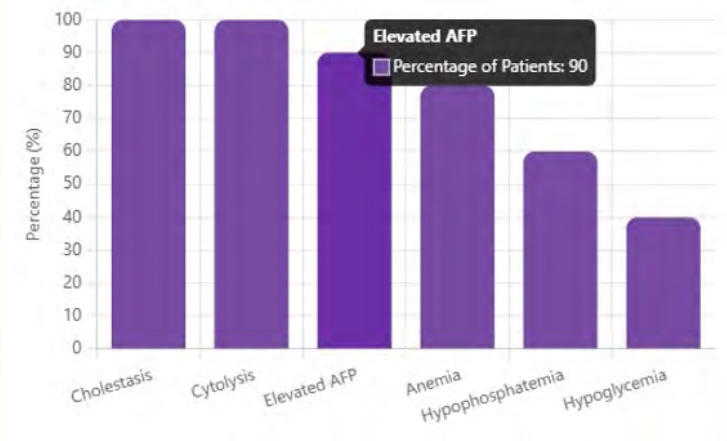

Figure 2: *Laboratory abnormalities.*

Amino acid chromatography revealed elevated tyrosine levels in blood and urine samples, with one patient (patient 4) showing elevation of both tyrosine and methionine in blood. Succinylacetone was elevated in blood and/or urine in all patients, with levels ranging from 40 to >336 µmol/L, confirming diagnosis in every case.

Radiological findings

Abdominal ultrasound was abnormal in all patients, with findings detailed in figure 3. Hepatic parenchyma patterns varied, showing homogeneous appearance in 50% (5/10), heterogeneous appearance in 40% (4/10), and multinodular pattern in 50% (5/10), with one case showing frank cirrhosis. Renal abnormalities included hyperechogenicity in 10% (1/10) and nephrocalcinosis in 10% (1/10). Ascites was present in 20% (2/10).

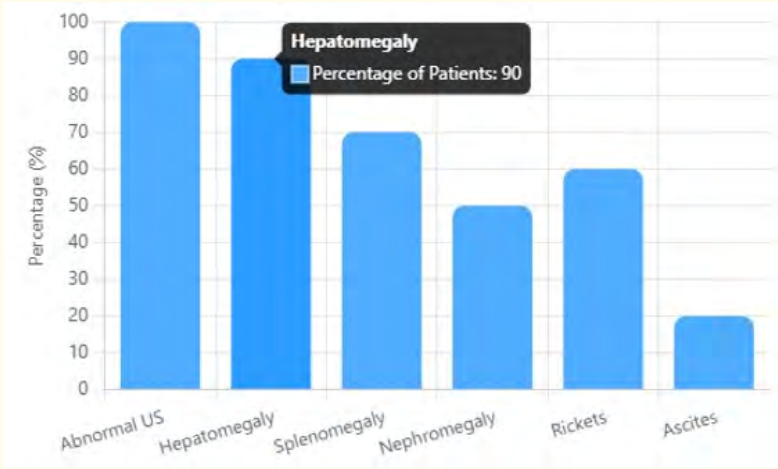

Figure 3: *Radiological findings.*

Advanced imaging was selectively performed. Abdominal CT in patient 7 confirmed heterogeneous multinodular hepatomegaly with bilateral nephromegaly. Abdominal MRI in two patients revealed multinodular hepatic lesions with homogeneous enhancement in one case, and cirrhotic liver changes with portal hypertension in another. Brain MRI in patient 8 showed changes consistent with probable vascular leukoencephalopathy.

Plain radiographs demonstrated rickets signs predominantly affecting metaphyses of long bones, consistent with hypophosphataemic rickets.

One patient underwent liver biopsy (patient 2), demonstrating chronic hepatopathy with cirrhosis and regenerative nodules, but no evidence of malignancy.

Treatment and outcomes

All patients were started on tyrosine- and phenylalanine-restricted diet, with 70% receiving specialised amino acid compositions. Nine patients (90%) received nitisinone therapy at 1 mg/kg/day in two divided doses. NTBC was initiated at mean age of 23.4 months (range: 6 months to 7 years 9 months). Mean delay between diagnosis confirmation and treatment initiation was 1.1 months (range: 1-3 months).

Symptomatic treatment included vitamin K supplementation in eight patients (80%). One patient (patient 10) received comprehensive supportive care including phosphorus supplementation, alfacalcidol, and potassium chloride, but did not receive NTBC and subsequently died. No patient underwent liver transplantation.

Clinical evolution was favourable in seven patients (70%), characterised by clinical, biochemical, and radiological improvement following treatment initiation. Two patients (20%) died of hepatic failure complicated by haemorrhagic syndrome. Patient 3 died eight days after NTBC initiation despite treatment, and patient 10 died at eight years without receiving NTBC therapy. One death occurred with concurrent cytomegalovirus infection. One patient (10%, patient 4) was lost to follow-up.

Mortality occurred exclusively in patients with severe acute presentation and was associated with delayed treatment initiation or inability to access NTBC therapy. All patients who received early NTBC treatment and maintained regular follow-up showed favourable outcomes.

Discussion

Hereditary tyrosinaemia type 1 (HT1) is an ultra-rare inborn error of metabolism, with an estimated global incidence of 1:100,000 - 1:120,000 live births, though higher rates are observed in populations with founder effects and high consanguinity [1]. This study represents the largest paediatric cohort of HT1 reported from Morocco and provides insights relevant to the wider MENA region.

Regional significance and genetic epidemiology

Consanguinity was universal in our cohort (100%), with first-degree consanguinity predominating (70%). This pattern reflects the genetic epidemiology common across North Africa and the Arabian Peninsula, where high rates of consanguinity increase the prevalence of autosomal recessive disorders. Comparable findings have been reported in Lebanon, where consanguinity was present in most HT1 families [4], and in Turkey, where founder effects have been described [5]. The high rate of consanguinity likely contributes to the clustering of cases within a single institution in Morocco, in contrast to regions with lower consanguinity rates. Comparison of HT1 characteristics across international cohorts is summarized in table 1.

Characteristic	Morocco (Current study, n = 10)	Lebanon[4] (n = 15)	Turkey[5] (n = 29)	Spain[6] (n = 46)
Study Period	2007-2024	2008-2020	1999-2016	1991-2018
Demographics				
Female predominance	60%	53%	48%	52%
Consanguinity rate	100%	>80%	High†	Not reported
Clinical Presentation				
Acute form	70%	67%	62%	43%‡
Mean age at diagnosis (months)				
- Acute cases	8.3	7.0	9.2	2.1‡
- Chronic cases	62.0	48.0	86.4	24.8‡
Common Clinical Features				
Hepatomegaly	90%	87%	97%	91%
Growth failure	90%	80%	83%	65%
Rickets	30%	27%	41%	15%
Laboratory Findings				
Elevated AFP	90%	93%	86%	89%
SA elevation	100%	100%	100%	100%
Treatment				
NTBC therapy rate	90%	60%§	86%	100%
Mean age at NTBC start (months)	23	36	28	6‡
Outcomes				
Favourable evolution	70%	67%	72%	96%‡
Mortality	20%	33%	14%	4%‡
HCC development	0%	7%	17%	2%

Table 1: *Comparison of HT1 characteristics across international cohorts.*

†Exact percentage not specified; ‡Significantly improved due to newborn screening; §Limited by treatment availability; HCC: Hepatocellular Carcinoma; AFP: Alpha-Foetoprotein; SA: Succinylacetone; NTBC: Nitisinone.

Clinical presentation and diagnostic challenges

The mean age at diagnosis in acute cases (8.3 months) was slightly later than in Lebanon (7 months) [4] and much later than in Spain, where systematic newborn screening has enabled early detection [6]. The predominance of acute presentation (70%) in our cohort mirrors populations without screening programs and contrasts with Spanish data, where earlier detection has shifted the spectrum toward milder forms with better prognosis [6].

Diagnostic delay was markedly different between presentations: 30 months in chronic cases versus 4.6 months in acute cases. By comparison, the Spanish cohort reported a median delay of only 6 days due to newborn screening [6]. These findings illustrate how disease severity and healthcare infrastructure shape diagnostic timelines.

Laboratory and radiological findings

Succinylacetone, the pathognomonic marker for HT1, was elevated in all patients, confirming its central role in diagnosis [1,3]. Elevated α-fetoprotein, found in 90% of our cases, supports its utility as both a disease biomarker and a surveillance tool for hepatocellular carcinoma risk.

Radiological findings-including hepatomegaly, splenomegaly, and nephromegaly-were consistent with Turkish [5] and Lebanese [4] cohorts. By contrast, the Spanish series reported fewer advanced abnormalities, highlighting the benefits of earlier diagnosis and treatment [6].

Treatment access and outcomes

Nitisinone therapy was available to 90% of our patients, representing a major improvement compared with earlier reports from resource-limited settings. This treatment rate was substantially higher than in Lebanon, where access was limited [4], and approached levels in Spain, where all patients received therapy [6].

The clinical response rate of 70% in our cohort was encouraging but reflects the consequences of delayed diagnosis. Mortality (20%) was lower than in Lebanon (≈33%) [4] but remained higher than in Spain, where newborn screening and early intervention have led to near-normal survival rates [6]. Long-term complications, including hepatocellular carcinoma and neurological crises, as reported in Turkey despite therapy [5], reinforce the importance of early diagnosis and consistent follow-up.

Importantly, the only patient who did not receive nitisinone died, underscoring the therapy's life-saving impact. Even a relatively short delay (mean 1.1 months) between diagnosis and treatment initiation may represent a critical window for disease progression.

International comparison and clinical implications

Cross-cohort comparisons highlight distinct challenges and opportunities. The Lebanese series demonstrated the effects of late diagnosis and limited therapy access [4], while the Turkish cohort emphasised the role of genetic counselling and family screening in consanguineous populations [5]. By contrast, the Spanish experience illustrates the transformative effect of nationwide newborn screening, enabling early treatment and dramatically improving outcomes [6].

Our findings highlight the need for:

- Increased clinician awareness of HT1 in Morocco, particularly in children from consanguineous families presenting with liver dysfunction.
- Integration of genetic counselling and family screening into standard care.
- Consideration of implementing newborn screening for HT1 in Morocco and across the MENA region, given its proven effect on outcomes.

Clinical recommendations for regional healthcare policy

1. Enhanced diagnostic awareness: Clinicians should maintain a high index of suspicion for HT1 in consanguineous families with unexplained liver disease.
2. Rapid diagnostic workup: Succinylacetone measurement should be prioritised as the definitive diagnostic test [1,3].
3. Universal treatment access: Equitable access to nitisinone must be ensured, as delayed or absent therapy significantly worsens outcomes.

4. Family screening and counselling: Systematic sibling testing and genetic counselling should be routine in populations with high consanguinity.
5. Multidisciplinary care: Management should involve specialised metabolic teams for dietary monitoring, complication surveillance, and long-term follow-up.

Study Limitations

Several limitations must be acknowledged. The retrospective design may have introduced selection bias, and the single-centre scope limits generalisability. The sample size, though the largest Moroccan series reported, restricts statistical power. Long-term data were incomplete, particularly for neurocognitive outcomes and hepatocellular carcinoma surveillance. Finally, the study period spanned 18 years, during which diagnostic tools and treatment strategies evolved, potentially affecting care consistency.

Future Directions

While nitisinone and dietary management remain the therapeutic cornerstone, curative approaches are under investigation. FAH gene delivery has shown promising preclinical results, restoring liver function and preventing disease progression in animal models [9]. Novel strategies such as nitisinone desensitisation for patients with hypersensitivity have also been reported [8], expanding future therapeutic options.

Conclusion

This study presents the largest paediatric cohort of HT1 from Morocco, highlighting the significant impact of consanguinity on disease prevalence and the challenges of late diagnosis in resource-limited settings. The universal presence of consanguinity underscores the importance of genetic counselling and family screening, with direct relevance for healthcare planning across similar populations in the Arabian Peninsula and broader MENA region.

Whilst nitisinone therapy was accessible to most patients and resulted in favourable outcomes in 70% of cases, the 20% mortality rate emphasises the critical importance of early diagnosis and treatment initiation. Our findings support the potential benefits of implementing newborn screening programmes for HT1 in Morocco and similar populations, particularly given the high consanguinity rates and genetic predisposition.

Enhanced diagnostic awareness amongst healthcare providers, improved access to specialised metabolic testing, and systematic family screening could significantly improve outcomes for children with HT1 in Morocco and similar settings. The comparison with international cohorts demonstrates that whilst challenges exist in resource-limited settings, significant improvements in patient outcomes are achievable through enhanced diagnostic capabilities and treatment access.

Enhanced regional collaboration through shared treatment protocols, joint newborn screening initiatives, and coordinated genetic counselling services could significantly improve outcomes for children with HT1 and other rare metabolic disorders across populations sharing similar genetic and healthcare challenges. Continued research and international collaboration are essential to optimise care for children with this rare but treatable condition.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

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