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CASE REPORT

A Case of Hb Quong Sze Co-Inherited Thai Deletion Resulting in Falsely Elevated HbA1c Values

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SUMMARY

Background: **Hb Quong Sze (Hb QS) is a rare Hb variant that, when combined with α^0-thalassemia, can produce Hb QS-H disease. Reports of Hb QS-H disease affecting HbA_{1c} testing are limited.**
Methods: **This study reports a case of Hb QS-H disease with abnormally elevated HbA_{1c} levels measured by the G11 high-performance liquid chromatography (HPLC) system. Three additional detection systems (D100, Capillary Electrophoresis [CE], and Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry [MALDI-TOF-MS]) were employed for comparative assessment of HbA_{1c} values. Hemoglobin analysis was performed using CE, while conventional thalassemia gene detection utilized Gap-PCR and PCR-reverse dot blot (RDB).**
Results: **The patient exhibited normal blood glucose levels (fasting: 4.18 mmol/L; 2-hour postprandial: 5.96 mmol/L), yet the G11 system recorded a markedly elevated HbA_{1c} value of 18.4%. Among the three alternative detection systems, the D100 system yielded a value of 2.38%, while both CE and MALDI-TOF-MS failed to provide valid HbA_{1c} measurements. Genetic analysis confirmed co-inheritance of Hb QS and Thai deletion in this patient.**
Conclusions: **Our findings demonstrate that Hb QS-H disease significantly interferes with HbA_{1c} quantification, with methodological variability observed across different detection platforms.**
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KEYWORDS

Hb Quong Sze, HbA_{1c}, Hb H, thalassemia

INTRODUCTION

Glycated hemoglobin (HbA_{1c}) is generated via the non-enzymatic attachment of glucose to the N-terminal valine of β-globin chains, making it a well-established indicator of average blood glucose levels over approximately 8 - 12 weeks [1,2]. The adoption of $HbA_{1c} \geq 6.5\%$ as a diagnostic threshold for diabetes gained global acceptance in 2010 [3]. Nevertheless, certain clinical conditions - such as hemoglobinopathy, recent transfusion events, renal impairment, and gestational states - can alter red blood cell survival, thereby affecting HbA_{1c} reliability [4]. Commercially available techniques for HbA_{1c} quantification encompass immunoas-

says, enzymatic methods, capillary electrophoresis (CE), cation-exchange high-performance liquid chromatography (HPLC), and boronic acid affinity chromatography [5]. Hb H disease, a severe α-thalassemia caused by mutations in three α-globin alleles, remains understudied in terms of its influence on HbA_{1c} accuracy. Current literature on Hb H disease's interference with HbA_{1c} measurements remains sparse, with conflicting results reported across analytical platforms [1,4,6].

In this study, we present a case of aberrantly elevated HbA_{1c} levels in a patient co-inheriting Hb Quong Sze (Hb QS) and the Thai deletion. Comparative analysis using three distinct methodologies showed inconsistencies in HbA_{1c} quantification, underscoring the critical impact of methodological variability in hemoglobinopathy populations.

CASE REPORT

A 32-year-old pregnant woman and her husband presented to our institution for routine first-trimester prenatal screening. Thalassemia is common in the southern Chinese region of Guangxi Zhuang Autonomous Region. In accordance with regional health policies, she was advised to undergo thalassemia screening. She was also screened for gestational diabetes.

Initial hematological evaluation revealed microcytic hypochromic anemia: hemoglobin (Hb) 80 g/L (normal range: 115 - 160 g/L), mean corpuscular volume (MCV) 82 fL (reference: 82 - 100 fL), and mean corpuscular hemoglobin (MCH) 20.3 pg (reference: 27 - 34 pg) (Sysmex XN 1000; Sysmex Corporation, Kobe, Japan). CE analysis demonstrated abnormal hemoglobin fractions: HbA 67.4%, HbA_2 0.4%, Hb H 31.5%, and Hb Bart's 0.7% (CapillaryS2 Flex Piercing; Sebia, Lisses, Paris, France). Biochemical testing showed total bilirubin 19.8 μmol/L, direct bilirubin 5.7 μmol/L, and indirect bilirubin 14.1 μmol/L. These data strongly suggested that the pregnant woman might be an α-thalassemia patient.

To confirm the presence of thalassemia, routine genetic analysis was performed. Gap-PCR identified common deletional mutations in Chinese populations ($--^{SEA}$, $--^{THAI}$, $-\alpha^{3.7}$, $-\alpha^{4.2}$), while PCR-reverse dot blot (RDB) detected non-deletional variants (Hb QS, Hb CS, Hb WS) (Yaneng Biotech, Shenzhen, China). The patient was ultimately diagnosed with Hb H disease (Hb QS/--THAI compound heterozygous α-thalassemia intermedia).

Notably, discordant metabolic parameters were observed in diabetes screening. Fasting plasma glucose 4.18 mmol/L (reference: 3.9 - 6.1 mmol/L) and 2-hour postprandial glucose of 5.96 mmol/L (reference < 7.8 mmol/L) fell within normal ranges. However, initial HbA_{1c} quantification via HPLC on G11 analyzers (Tosoh Corporation, Shunan, Yamaguchi, Japan) yielded an aberrantly elevated value of 18.4% (reference ≤ 6.5%). Repeat testing with an alternative HPLC system D100 (Bio-Rad, Hercules, CA, USA) produced 2.38%. Surprisingly, neither CE nor Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry (MALDI-TOF-MS) could detect measurable HbA_{1c}. These method-dependent discrepancies strongly indicate hemoglobinopathy interference with HbA_{1c} quantification.

DISCUSSION

The interference of hemoglobinopathies with HbA_{1c} measurement has been predominantly reported in cases involving hemoglobin variants affected by methodological limitations [7,8]. In contrast, reports documenting such interference in thalassemia syndromes, particularly Hb H disease, remain scarce. In the present study, we unexpectedly identified markedly elevated HbA_{1c} levels in a pregnant woman undergoing routine prenatal screening. This pregnant woman was finally confirmed not to have diabetes, but was detected with Hb QS combined with Thai deletion and diagnosed with Hb QS-H disease.

Hb QS arises from a CTG→CCG mutation in the HBA_2 gene, leading to a leucine-to-proline substitution at the amino acid level. This variant demonstrates α^+-thalassemia-like phenotypic characteristics. Notably, when co-inherited with α^0-thalassemia, it can manifest as non-deletional Hb H disease [9]. Despite its clinical significance, the population prevalence of this hemoglobinopathy remains remarkably low. Epidemiological data from Huizhou City, Guangdong Province revealed only 521 carriers (0.45%) among 113,400 thalassemia-positive screening samples [10]. This scarcity explains the limited documented cases of Hb QS-H disease and the paucity of research investigating its potential interference with HbA_{1c} quantification. Nevertheless, considering the severe hematological complications associated with its coinheritance with α-thalassemia, Hb QS has been incorporated into standardized commercial detection panels in China. These diagnostic kits are now routinely implemented in clinical laboratories nationwide, reflecting the government's proactive approach to managing this rare but clinically consequential variant.

Previous studies have reported that HbA_{1c} levels in Hb H disease patients tend to be falsely decreased [6]. This phenomenon may be attributed to shortened erythrocyte lifespan (typically < 90 days), which significantly reduces the time available for hemoglobin glycation [4]. In the current study, the G11 analyzer demonstrated falsely elevated HbA_{1c} values, likely due to incomplete separation between the Hb H peak and HbA_{1c} peak during chromatographic analysis, resulting in measurement interference [11]. In contrast, the D100 system showed better resolution without evident peak overlap, though the measured HbA_{1c} values remained lower than those observed in deletional Hb H disease [6]. For non-deletion Hb H disease variants, CE methods also exhibited measurement inaccuracies. Specifically, the Hb Barts peak showed electrophoretic migration overlapping

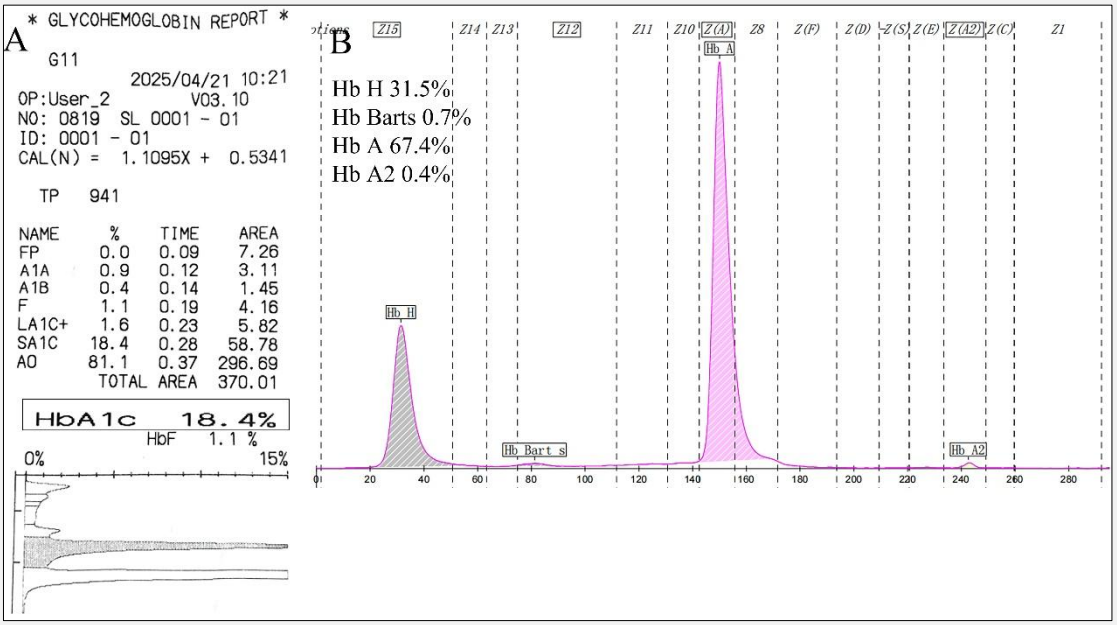

Figure 1. A) HPLC (C11 system) analysis of HbA_{1c} results in this patient, B) Hb analysis of this patient by CE.

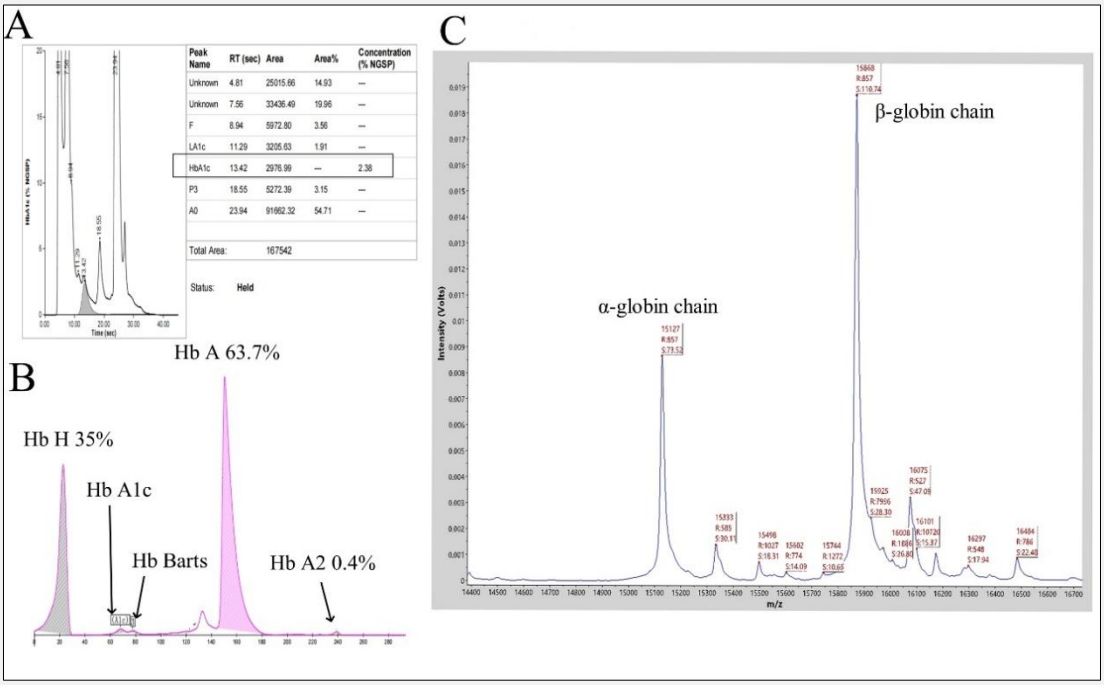

Figure 2. A) HbA_{1c} measurement results by HPLC (D100 system), B) CE, and C) MALDI-TOF-MS in this patient.

HPLC suggested a HbA_{1c} of 2.38%, which could not be quantified by CE and MALDI-TOF-MS.

with the HbA_{1c} peak, making precise quantification impossible. Similarly, MALDI-TOF-MS showed undetectable HbA_{1c}, likely reflecting suboptimal analytical sensitivity for low-concentration targets. Our comparative analysis of four detection platforms in Hb QS-H disease revealed significant inter-method variability, highlighting the critical importance of methodological selection when screening and monitoring diabetes in patients with hemoglobinopathies.

CONCLUSION

This study reports a case of Hb QS-H disease where the G11 platform yielded erroneous HbA_{1c} measurements, while contradictory results were obtained from three other analytical platforms. These findings underscore the critical importance of employing multiple analytical methodologies when screening and monitoring diabetes in patients with hemoglobinopathies. When HbA_{1c} measurements prove to be unreliable, a comprehensive diagnostic strategy is necessary, including continuous glucose monitoring, oral glucose tolerance testing, or other alternative testing indices.

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Declaration of Interest:
The authors report no conflicts of interest relevant to this article.

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