The Prevalence and Incidence of Atypical Hemolytic Uremic Syndrome in Iran: A Systematic Review and Meta-Analysis Protocol Study

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Abstract

Context: Hemolytic uremic syndrome (HUS), being more prevalent in infants and children, is recognized by a triad of acute kidney injury, microangiopathic hemolytic anemia, and thrombocytopenia. It is classified according to the underlying disorders, such as infection, systemic, metabolic disorder, or complement dysregulation. It has a high rate of morbidity and mortality. Many types of treatment, such as conservative management, plasma exchange, regular plasma infusion, and even a new expensive medication, "Ecluzimab", have been suggested. The aim of this systematic review is to estimate the incidence and prevalence of HUS (according to diarrhea positive or negative samples). In addition, the study will investigate the clinical presentation and the outcome of Iranian patients.

Evidence Acquisition: The following data bases will be explored for articles published between years 1985 and 2016, PubMed, EMBASE, OVID, SCOPUS, Web of Sciences, Google Scholar, Google, barakatkns.com, MagIran, SID, dociran, PDFiran, and ganj.irandoc. Besides, all online university databases will be searched for theses and abstracts of local or international congresses; a manual search will be performed to identify pertinent cross references. Systematic review or meta-analysis, longitudinal and cohort studies, cross-sectional, case-control, and epidemiological studies will be included in this review. Relevant conference proceedings, theses or unpublished data will also be considered. The retrieved data should comprise of proportions, incidence, prevalence, geographical distribution, mortality and morbidity rates (i.e. dialysis and central nervous system involvement). A meta-analysis will be performed if 3 similar studies are found. If sufficient data is extracted, subgroup analysis will be performed for age, gender, acute kidney injury, dialysis, and death.

Results: The results of the current study could have implications for health policies, practice, research, and medical education: The data could improve clinical and health care decisions, allow estimation of the number of patients that require new medication, and could direct future research design in this field.

Keywords: Hemolytic- Uremic Syndrome, Atypical Hemolytic Uremic Syndrome, Diarrhea Prodrom Positive HUS

1. Context

Hemolytic uremic syndrome (HUS) is defined by thrombocytopenia, acute kidney injury, and microangiopathic hemolytic anemia. Historically, it was identified by a positive diarrhea and negative HUS. Atypical hemolytic uremic syndrome (aHUS) is an old terminology used for describing non-infectious-induced HUS in infants and children (1). Gaining an understanding of the concealed mechanisms and pathophysiology, different etiologies, including bacteria or viral infections, metabolic disorders, vacuities, medication, and complement dysregulation have been identified (2-5).

Hemolytic uremic syndrome is one of the leading causes of acute kidney injury in Iranian children (6, 7). Delayed improvement of kidney function has been reported (8). This was found in approximately one third of cases who died (9, 10). Furthermore, HUS affects various organs and there is a few studies on morbidity in Iranian children: i.e. cholelithiasis presented with obstructive jaundice (11), delayed dilated cardiomyopathy responded to inotropic agents and diuretics (12), and diffuse brain ischemia (13), Gastrointestinal perforation, intussusceptions, and gangrene lead to surgical exploration (14).

The overall incidence of diarrhea negative HUS is 0.5 to 2.1 per 100000 per years (15, 16). The incidence rate of HUS /1000000 person-years was reported as 2.7 in the US, 2.1 in United Kingdome, and 2.1 in Canada (17). European registry of aHUS reported a pediatric prevalence of 3.3 cases one million individuals (18). Karimi et al. reported a declining incidence of HUS in Southwest of Iran with an annual incidence of 8 cases per one million children younger than 15 years in 1993 to 1.1 in 2003 (19). The overall mortality rate of HUS in Iran is high, between 19.5% and 35% (20).

2. Research Question and Analytic Framework

The proportion, prevalence, and incidence of HUS (D positive and negative HUS) in Iran will be estimated in this review. Moreover, the etiology and final outcome of HUS will be studied.

3. Protocol and Registration

The protocol has been registered with the international prospective register of systematic reviews (PROSPERO) (21), registration number CRD42017059086 , and approved by the ethics committee of Iran University of Medical Sciences, number code: 96-02-225-31405. The Preferred

Reporting Items for systematic review and meta-analysis (PRISMA)-Protocols statement was followed through the study.

4. Eligibility Criteria

All patients with hemolytic uremic syndrome or renal biopsy indicating typical pathological findings of thrombotic microangiopathy (TMA) will be included. The definition of hemolytic uremic syndrome is microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure. All cases with atypical (diarrhea negative), diarrhea positive hemolytic uremic syndrome, and TMA will be included. Microangiopathic hemolytic anemia is identified by hemoglobin of less than the lower limit of normal for age, high reticulocyte count, elevated level of lactic dehydrogenase (LDH) when the coombs test is negative. Thrombocytopenia is defined by platelet count of less than 150000/micro liters, and renal injury is delineated by serum creatinine of more than the upper limit of normal for age. This study will include systematic reviews or meta-analysis, longitudinal and cohort studies, cross-sectional, case-control, and epidemiological studies. Pertinent conference proceedings, theses or unpublished data will also be evaluated. Experimental studies, narrative reviews, and case reports, and thrombotic thrombocytopenic purpura will be excluded.

5. Types of Participants

The outcome of interest is the proportion of aHUS, final outcome including end stage renal disease (ESRD), morbidity, or death.

6. Data Source and Search Strategy

The following data bases will be searched for published articles, PubMed, EMBASE, Google Scholar, Google, OVID, SCOPUS, Web of Sciences, barakatkns.com, MagIran, SID, dociran, PDFiran, and ganj.irandoc. Moreover, databases of each medical university in Iran will be searched for relevant theses and records. In order to obtain missed data, a manual search will be performed for cross references, the abstracts of international, regional, or local congresses. The authors will be contacted to obtain more details in case of missing information and to collect unpublished data from known Iranian investigators pundit in HUS. Studies issued between January 1985 and January 2016 will be considered. Before the final analyses the researchers will repeat the search for recent admissible studies to be covered in the review.

7. Provisional Search Strategy for Pubmed

Atypical hemolytic uremic syndrome "(Mesh) AND "Iran"(Mesh)/"Hemolytic-Uremic Syndrome"(Mesh)) AND "Iran"(Mesh)/"Thrombotic Microangiopathies"(Mesh) AND "Iran"(Mesh)/ ("glomerulonephritis"(MeSH Terms) OR "glomerulonephritis"(All Fields)) AND "Iran"(Mesh).

"acute kidney injury"(MeSH Terms) OR Acute renal failure, "renal insufficiency, chronic"(MeSH Terms), chronic"(MeSH Terms) OR chronic renal disease, "renal dialysis"(MeSH Terms) OR "dialysis"(MeSH Terms).

The comparable Persian terms for the above quoted words will be used to survey the articles in Iranian database.

8. Study Selection

After the preliminary pilot search, NH, MS, and FJ will independently review the abstracts and articles to select suitable studies. Disagreement between reviewers will be solved by consensus or by NH. The STROBE statement will be used to assess the quality of studies and their eligibility as previously explained (22, 23). The researchers will use PRISMA flowchart to present the process of article selection.

9. Data Extraction and Risk of Bias Assessment

The researchers have designed a structured data abstraction form and one author will extract data that including authors' name, title of study, journal, year, volume, number, page; language of study, center of study, type of study, period of study, sample size, patient information (age, disease and gender), the region of study, length of follow up, outcome (recovery, HUS, death and unreported), and funding sources.

Three reviewers will independently assess the risk of bias by using the tool developed by Hoy et al. (22-24). Disagreement between reviewers will be solved by consensus or by the third author (NH).

10. Data Synthesis and Statistical Analysis

The authors will consider performing meta-analyses when at least 3 studies of low or medium risk of bias exist and have similar population, design, and outcomes. The researchers are aware of the probable biases of meta-analyses that include a small number of articles; before calculating a pooled summary estimate in a meta-analysis, the researchers will carefully consider the heterogeneity across studies. An anecdotal synthesis of the data will be given. The researchers will calculate point prevalence and incidence. If studies could be assembled, the researchers will pool results for studies that have used the same technique and the same outcome. A random-effects meta-analysis and risk ratios for binary outcomes will be used. The researchers will calculate 95% confidence intervals.

If the studies cannot be clustered, both the Chi-square test (P value of 0.1 set for clinical significance) and the I-squared statistic will be used to evaluate heterogeneity between the studies in effect measures (I-squared value of more than 50% indicates substantial heterogeneity) (25). The researchers will investigate the potential causes for heterogeneity. Funnel plots and Kendall's test will be used to gauge publication bias.

If data are sufficient, the researchers will conduct subgroup-analyses testing for differences between age groups (children-adults), regions, diarrhea positive and negative, acute kidney injury, and chronic kidney disease.

11. Discussion

This protocol aims at investigating the incidence of hemolytic uremic syndrome and its subtypes in Iran. The review will focus on morbidity (chronic kidney disease and ESRD) and mortality.

There are currently no figures of HUS incidence or prevalence in Iranian children. The epidemiological study of HUS would help promote laboratory methods to accelerate the most accurate diagnosis of the underlying disease, as different types of HUS have various pathogenesis and management (26).

Delay in diagnosis and treatment has a crucial impact on quality of life and increases the risk of morbidity and mortality (27, 28).

No surveillance strategy has been conducted to detect shiga-toxin in suspicious diarrhea cases in Iran so far. Correct and on time diagnosis is decisive for appropriate management and follow up. In addition, a few centers in Iran afford to measure complement component to detect atypical HUS due to complement dysregulation. However, relying on this approach per se has its limitations and drawbacks. The panel is not complete yet and a normal result does not eliminate neither inherited nor acquired complement dysregulation type of HUS. An accurate diagnosis is paramount to reduce morbidity with on time treatment using novel medication that inhibit terminal component. The findings of this systematic review will be published in a peer-reviewed journal and presented in conferences. This systematic review and meta-analysis will estimate the frequency of HUS (D+ or D-) in Iran. This figure could help clinical and health care administrative processes. Furthermore, it could assist with the unfolding of the path for forthcoming research design and direction in this field.

12. Implication for Health Policy, Practice, Research, and Medical Education

The proposed research could improve clinical and health care decisions, allow estimation of patients requiring new medication, and direct future research design in this field.

Footnote

Conflict of Interest: None.

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