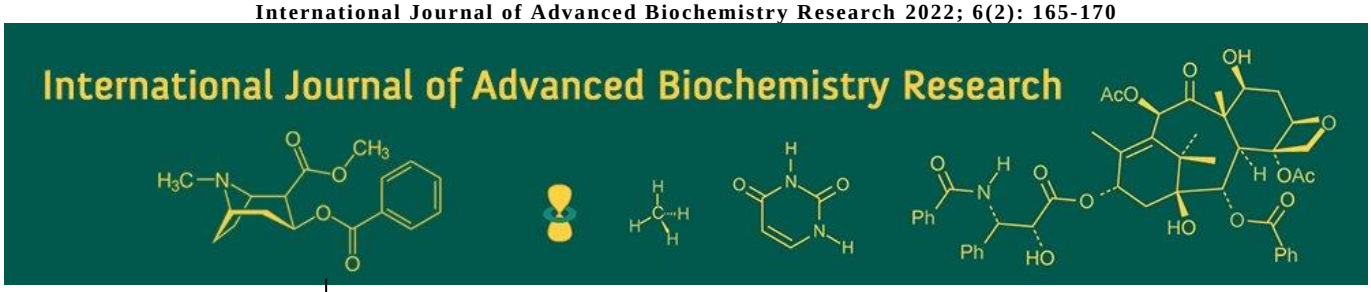

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Biochemical and hematological profiles of subjects with cryptogenic ischemic stroke

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Abstract
Cryptogenic ischemic stroke refers to a DVA for which no specific cause has been detected after adequate investigation. It is an emerging concept whose increasing frequency is currently a public health problem. Thus, the objective of this study was to determine the biochemical and hematological profiles of subjects with cryptogenic ischemic stroke.
This is a descriptive and analytical study of patients with cryptogenic stroke followed at the neurological clinic of the CHNU of Fann. The study included 40 patients matched to 40 healthy controls according to sex and age ±2 years. All biochemical parameters were measured with the Architect ci4100 (Abbott, Chicago, USA) using enzymatic techniques and hematological parameters were measured with the XN-1000 (Sysmex, France).
The study population consisted of 40 subjects with cryptogenic ischemic stroke. The mean age of our patients was 47 ± 11 years and the sex ratio was 1.35. The main cardiovascular risk factors found were hypertension (45%), dyslipidemia (23%) and diabetes (15%). Evaluation of biochemical parameters showed significant differences in HDL-C (p<0.0001) and LDL-C (p<0.0001). Hyperuricemia was the most frequent biochemical abnormality (47%) followed by hypercholesterolemia (20%). Hematological abnormalities were mainly anemia (22%), lymphocytosis (35%) and platelet line abnormalities (15%).
The results obtained suggest that the profile of biochemical and hematological parameters is associated with several disturbances including anemia, hyperuricemia, and lymphocytosis, thus showing the high susceptibility of stroke subjects to multiple infections.

Keywords: Ischemic stroke, cryptogenic, biochemical profile, hematological profile

Introduction
According to the World Health Organization (WHO), stroke is defined as "the rapid development of localized or global signs of cerebral dysfunction with symptoms lasting more than 24 hours, which can lead to death, without any apparent cause other than a vascular origin" [1].
In France, as in other industrialized countries, stroke is the third leading cause of death after cancer and cardiovascular diseases [2]. In Senegal, they are the leading cause of neurological diseases. They are responsible for 2/3 of the mortality in neurology departments in Dakar [3].
The occurrence of stroke is favored by known cardiovascular risk factors that can be prevented. Control of risk factors such as hypertension, diabetes, dyslipidemia and smoking is essential [4]. They are sometimes linked to a poor lifestyle (smoking, obesity...), but other unknown etiological circumstances seem to be linked to the occurrence of ischemic stroke, especially when the cause is unknown [5]. This type of stroke, for which no specific cause has been detected after adequate investigation, is called cryptogenic ischemic stroke or stroke of undetermined etiology according to the TOAST classification [6].
It has been reported that about 25% of ischemic strokes are cryptogenic and these occur in 40% of young patients (< 50 years). A French stroke study found a 52.7% rate of cryptogenic infarcts in patients aged 16 to 44 years and a 30% rate in patients aged 45 to 54 years [7]. Cryptogenic infarcts thus represent the majority of cerebral infarcts in young subjects and thus constitute a real management challenge.

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The relevance of the problem of studying cryptogenic ischemic stroke is explained, in addition to its increasing frequency, by the lack of evidence to guide secondary prevention treatment after cryptogenic ischemic stroke. As a result, the risk of recurrence is considerably high [6].
Thus, the objective of this study was to evaluate the biochemical and hematological profiles in subjects with cryptogenic ischemic stroke.

Materials and Methods

Ethical approval

This study was approved by the Research Ethics Committee (REC) of Cheikh Anta Diop University (UCAD) in accordance with the rules set forth by the National Health Research Ethics Committee (CNERS) of Senegal under the number: 0412/2019/CER/UCAD.

Setting and type of study

This is a case-control study of subjects with cryptogenic ischemic stroke. Patients were recruited at the neurological clinic of the National University Hospital of FANN (CHNU/FANN) in Dakar/Senegal. Biochemical and hematological parameters were measured in the biochemistry laboratory of CHNU/FANN.

Study Population

Our study included 40 subjects with DVA of cryptogenic origin, according to the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification, referred to as Embolic Stroke of Undetermined Source (ESUS) [8]. DVA was diagnosed on clinical grounds and confirmed by CT data in all patients, and the cryptogenic origin was confirmed by the absence of high-risk emboligenic heart disease and extra- or intracranial steno sing atheroma (> 50%). Subjects with stroke related to patent foramen oval-interatrial septal aneurysm (PFO-ASIA), no stenotic (< 50%) potentially embolic atheroma, dissection, vasculitis, and small cerebral artery disease (≤ 2.0 cm) were not included in the study. Healthy control subjects matched for sex and age ± 2 years were recruited, and blood samples were collected under the same conditions as the cryptogenic ischemic stroke subjects. Blood was collected for each subject in a tube with lithium heparinate, a dry tube, and an EDTA tube. They were immediately transported on ice to the laboratory and then handled or stored at -20 °C until the day of handling. Data analysis was performed with XLSTAT version 2021 software and a value of $p < 0.05$ was considered a statistically significant difference.

Results

The study population consisted of 40 subjects with cryptogenic ischemic stroke. The mean age of the population was 47±11 years with extremes of 21 and 70 years and the sex ratio was 1.35. Among the cardiovascular risk factors studied, hypertension was the most frequent parameter with a rate of 45%, followed by dyslipidemia (23%) and diabetes (15%). Regarding the patients' lifestyle, smoking, alcoholism, and drug use were estimated at frequencies of 25%, 15%, and 5%, respectively (Table I).
Evaluation of hematological parameters in patients with cryptogenic ischemic stroke showed a mean red blood cell value of 4.71±0.64 10^3/µL with extremes of 3.37 and 6.01 10^3/µL associated with a mean hemoglobin level of 13.37±2.13 g/dL with extremes of 7.5 and 17.5 g/dL. The mean platelet value was 284.8 ± 84.28 10^3/µL with a minimum value of 122 10^3/µL and a maximum value of 601 10^3/µL. For white blood cells, a mean of 6.03 ± 1.97 10^3/µL was noted with extremes of 2.98 and 13.65 10^3/µL (Table II).

Table 1: General characteristics of the study population

	cryptogenic ischemic stroke	controls
Included	40	40
Average age (years)	46.97 ± 11	50.77 ±12
Sex ratio	23/17 (1.35)	23/17(1.35)
Diabetes%	15	-
HTA%	45	-
Dyslipidemia%	23	-
Migraine%	62	-
Sickle cell disease%	2	-
Smoking%	25	-
Alcoholism%	15	-
Drug abuse%	5	-
Sedentary lifestyle%	25	-

Table 2: Assessment of hematological parameters in cryptogenic ischemic stroke subjects compared to controls

	Cryptogenic Ischemic Stroke	controls	P
RBC (10^3/µL)	4,71 ± 0,64	4,84 ± 0,49	0,507
Hb (g/dl)	13,37 ± 2,13	14,16 ± 1,42	0,209
HT (%)	40,69 ± 8,13	42,46 ± 3,83	0,620
MCV (µm³)	88,15 ± 7,1	88,04 ± 5,32	0,485
MCHC (g/dl)	31,72 ± 2,13	33,35 ± 1,41	<0,0001
platelets (10^3/µL)	284,8 ± 84,28	273 ± 64,04	0,427
GB (10^3/µL)	6,03 ± 1,97	7,01 ± 1,67	0,005
Monocytes (10^3/µL)	0,73 ± 3,37	0,62 ± 0,20	0,087
Lymphocytes (10^3/µL)	3,39± 1,19	2,44 ± 0,71	< 0,0001
Granulocytes (10^3/µL)	4,2 ± 1,4	4,01 ± 1,5	0,296

RBC: Red blood cells, Hb: Hemoglobin, Ht: Hematocrit, MCV: Mean corpuscular volume, MCHC: Mean corpuscular hemoglobin concentration, WBC: White blood cells.
Comparison of hematological parameters between cases and controls showed a no significant decrease in mean red blood cell count in stroke subjects compared with controls ($p = 0.507$). Analysis of the platelet count results showed a non-significant increase ($p = 0.427$) in the mean platelet count in stroke patients (284.8±84.28 10^3/µL) compared with controls (273±64.04 10^3/µL). We found a significantly lower mean white blood cell value in stroke patients compared with controls with 6.03±1.97 10^3/µL versus 7.01±1.67 10^3/µL ($p < 0.001$) (see Table II).
Analysis of hematological abnormalities revealed mainly lymphocytosis (35%) followed by monocytosis observed in 23% of patients. Concerning the erythrocyte lineage, anemia was found in 22% of the study population. We also noted thrombocytosis in 5% of the study population and thrombocytopenia in 10% of the patients (Figure 1).

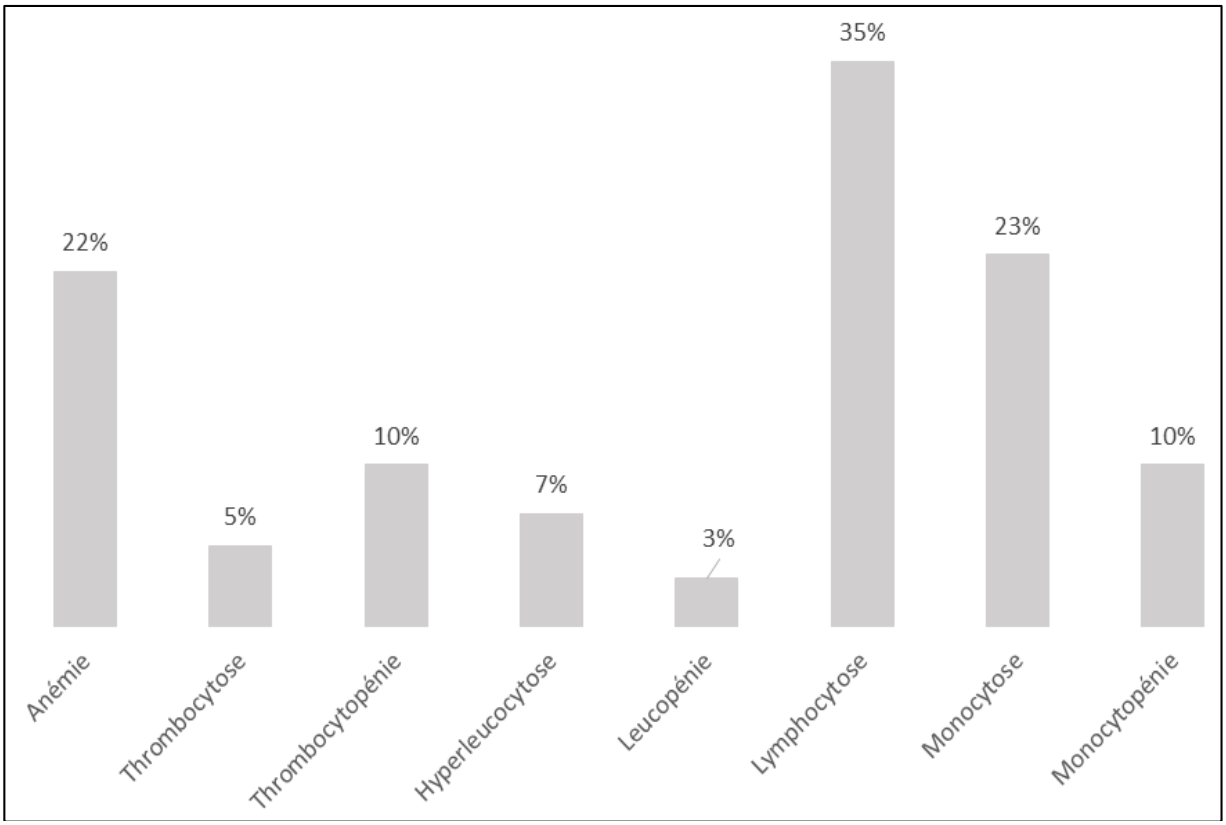

Fig 1: Frequency of hematological disturbances in cryptogenic stroke subjects

Analysis of biochemical parameters showed a mean value for fasting blood glucose of 0.96 ± 0.18 g/L with extremes of 0.68 and 1.90 g/L. The analysis of lipid parameters showed a mean total cholesterol value of 1.97 ± 0.69 g/L, a mean HDL cholesterol value of 0.46 ± 0.13 g/L and a mean LDL cholesterol value of 1.05 ± 0.49 g/L. The mean triglyceride value was 0.87 ± 0.39 g/L with extremes of 0.68 and 2.67 g/L. Comparison of lipid parameters between cases and controls showed statistically significant differences only for HDL-cholesterol and LDL-cholesterol with p values < 0.0001.

Assessment of renal function in the entire study population showed a mean glomerular filtration rate (GFR) value (with the MDRD formula) equal to 131 ± 24 ml/min/1.73m² in stroke patients (p = 0.256). The mean uric acid value was 55.3 ± 12.24 mg/L in stroke patients versus 48.18 mg/L in controls. Comparison of these mean values did not reveal a statistically significant difference (p = 0.009). Analysis of hs CRP values showed a mean value of 3.44 ± 2.64 mg/L in stroke patients versus 2.08±2 mg/L in control subjects (p = 0.002), (see table 3).

Table 3: Assessment of biochemical parameters in cryptogenic ischemic stroke subjects compared to controls

	AVCI Cryptogénique	Témoins	P
Total Cholesterol (g/L)	1.97	1.96	0.904
HDL Cholesterol (g/L)	0.46	0.59	0.353
LDL Cholesterol (g/L)	1.05	1.29	0.762
Triglycerides (g/L)	0.87	0.78	0.725
Fasting blood glucose level (g/L)	0.96	-	< 0.0001**
Urea (g/L)	0.22	0.16	0.007**
Creatinemia (mg/L)	7.43	7.98	0.254
Uric acid (mg/L)	55.95	48.07	0.912
CRP hs (mg/L)	3.41	1.92	< 0.0001**

The results of the biochemical parameters showed that hyperuricemia was the most frequent abnormality (47%), followed by hypercholesterolemia (20%) and increased us CRP (> 3 mg/L) with a rate of 20% (Figure 2). Hyperglycemia was the least common biochemical disturbance found in cryptogenic ischemic stroke with a frequency of 5%.

Discussion

Cryptogenic ischemic stroke is an emerging concept that refers to a stroke for which no specific cause has been detected after adequate investigation. It constitutes a diagnosis of elimination, with a significant risk of selection bias by underdiagnosing other etiologies. Today, several definitions are proposed, including the TOAST classification used in this study.

Cryptogenic ischemic stroke was characterized in our study by the early onset of the disease, with a mean age of 47 ± 11 years. This result is close to that found in the studies of Mathieu Zuber *et al.* [9] and Putala J *et al.* [6], which confirmed that more than 40% of cryptogenic strokes occur in subjects younger than 50 years. However, a study conducted in France found a slightly higher average age of 57 ± 13 years [10]. In developed countries, ischemic strokes occur 10 to 20 years later according to studies conducted in Japan and Norway [3, 4]. This disparity seems to be related to the higher life expectancy in industrialized countries and to the etiological factors that contribute to the occurrence of stroke.

Arterial hypertension (AH) was found in 45% of our patients. The results we obtained are in agreement with the data in the literature, which show that hypertension is the most common modifiable risk factor in the occurrence of stroke [3, 5, 11]. Indeed, hypertension multiplies the risk of cerebral infarction by 4 and of hemorrhage by 10 [6].

The evaluation of biochemical parameters showed that hyperuricemia was the most frequent abnormality with a rate of 47%. The mean value of uricemia was 55.30 mg/L and the comparison with that of the controls (48.18 mg/L) showed a significant difference with a value of $p = 0.009$. Our results were similar to those reported by several authors [12]. According to these authors, uric acid levels increase with diet and age. This increase is currently associated with cardiovascular events and many other metabolic abnormalities [13]. Many authors have also reported that hyperuricemia is the cause of microvascular anomalies responsible for the alteration of cerebral arteriolar regulation [14].

The comparison of renal parameters between cryptogenic ischemic stroke patients and controls showed a significant difference between the mean values of creatinemia (P= 0.036) and urea ($p = 0.015$) without significantly affecting the GFR ($p = 0.256$). A decreased GFR was found in 13% of the study population. According to some authors, renal insufficiency negatively influences the evolution of ischemic stroke. Indeed, the state of renal function in patients with acute stroke is a prognostic factor for severity [15]. Recently, several studies had shown that chronic kidney disease was associated with a high risk of stroke. A decrease in GFR would increase the risk of stroke by 43% without dialysis [16].

Assessment of us CRP, as a cardiovascular risk factor, had shown an increase in 20% of the study population. These results are similar to those of the study by Nizar *et al.*, which showed a frequency of 31% [17]. CRP us has been shown to be a prognostic factor in ischemic stroke; indeed, elevation of CRP us would reflect the severity of the ischemic stroke in the acute phase [18].

The study of the hematological profile showed anemia in 22% of the population, platelet lineage abnormalities in 15% of the subjects, and lymphocytosis was observed in 35% of the study population. These results were superimposed on those of the study by Kamadore *et al.*, who found a frequency of 21% for anemia [19]. Studies have shown that anemia diagnosed in stroke patients is associated with a higher risk of death up to 1 year after hospital admission [20]. In addition, stroke is also associated with an increased risk of infections, especially pneumonia and urinary tract infections [21].

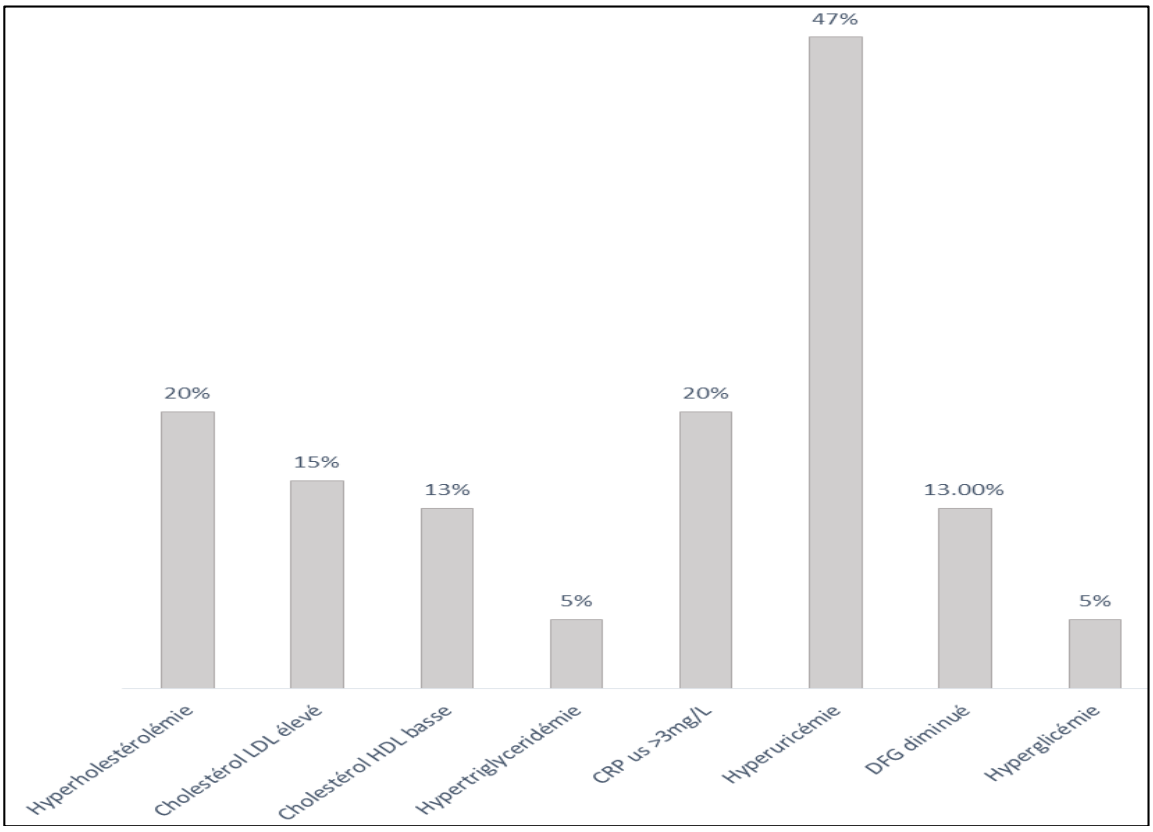

Fig 2: Frequency of biochemical disturbances in subjects with cryptogenic stroke subjects

Conclusion

The results obtained suggest that the profile of biochemical and hematological parameters is associated with several disturbances including anemia, lymphocytosis with a high risk of infections, hyperuricemia and hypercholesterolemia. If left untreated, these may lead to complications of the disease or even be factors in recurrence in subjects with cryptogenic ischemic stroke.

Authors' Declaration

The authors declare having no conflict of interest in related to this article.

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