

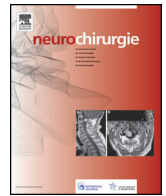


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Original article

## Subclinical haemorrhage in non-functional adenomas

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### ABSTRACT

**Aim.** – The prevalence and risk factors of subclinical haemorrhage on non-functional adenomas (NFA) remain controversial. The primary aim of our study was to assess the incidence of subclinical haemorrhage (SH) and the secondary objectives were to evaluate the risk factors of SH and the impact of SH on pituitary function at diagnosis.

**Patients and methods.** – This retrospective transversal analysis included 95 patients between January 2012 and December 2014. The patients included in this series were all adults (> 18 years of age), who presented a non-functional adenoma confirmed by an endocrinological evaluation and on dedicated MRI pituitary imaging. Sixty-four patients were eligible for this study. Subclinical haemorrhage was defined by the presence of haemorrhage within pituitary adenoma confirmed by pituitary MRI with no clinical symptoms. A senior neuroradiologist blinded to the diagnosis reviewed all MRI. The population was prospectively divided into two groups based on MRI results (SH group vs. group control) to determine risk factors.

**Results.** – SH was diagnosed in 22 patients (34.38%). No risk factors (age, sex, tumor size, chronic hypertension, diabetes mellitus, malignant disease, the use of anticoagulation or antithrombotic medication or Cabergoline treatment) were involved as regards the SH. At the diagnosis, pituitary deficiency was statistically significantly more frequent in the SH group (45.45%) than in the control group (19.04%) ( $P = 0.04$ ).

**Conclusion.** – The SH within NFA was observed in 34.38% of cases without an association of risk factors.  
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## 1. Introduction

Fortuitous discovery of an intra-tumor haemorrhage on dedicated pituitary MRI of pituitary adenomas with no clinical symptoms of pituitary apoplexy is quite common. These radiological, but clinically asymptomatic, observations are called subclinical haemorrhage (SH) [1–6]. SH was defined by the presence of haemorrhage within a pituitary adenoma confirmed on pituitary MRI with no clinical symptoms. The incidence of SH was estimated to be from 14 to 25%. An increase of hypopituitarism was observed in presence of the SH [1,2]. In contrast to an apoplexy defined as symptomatic haemorrhage, the risk factors and the consequences of SH have been rarely assessed in the literature [1,4,5,7–9]. Nevertheless, physicians are currently confronted with this discovery

due to the technological advances in radiological imaging. Many questions still remain regarding the natural history of SH as well as the management of risk factors for these patients in particular as regards anticoagulation or antithrombotic medication.

The primary objective of our study was to evaluate the incidence of subclinical haemorrhage (SH) and the secondary objectives were to evaluate the risk factors of SH and the impact of SH on pituitary function at the diagnosis.

## 2. Patients and methods

### 2.1. Study design

This retrospective transversal study concerned 95 consecutive patients with non-functional adenoma. Data on these patients were collected over a period of 3 years (January 2012 to December 2014) and identified from the institution-collected database. All patients

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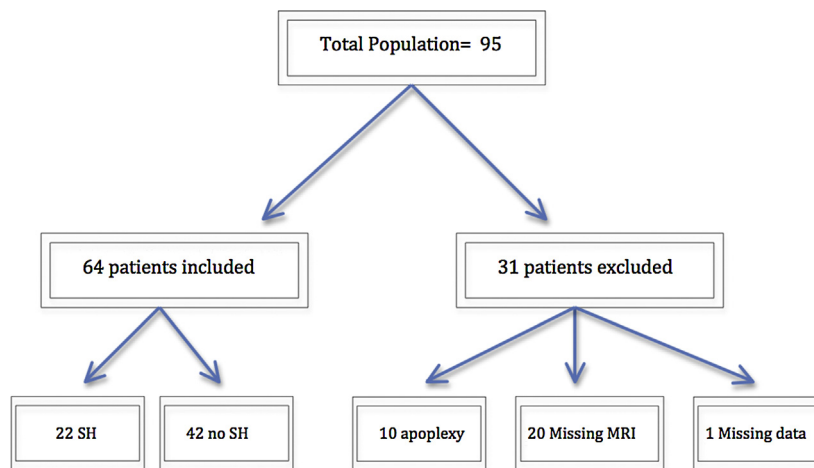


Fig. 1. Flowchart of patients included. SH: subclinical haemorrhage; no SH: control group.

were seen in consultation at the Neurosurgery and Endocrinology Departments of Strasbourg University Hospital.

The primary objective was to assess the incidence of SH and the secondary objectives were to evaluate the risk factors and the impact of SH on pituitary function at diagnosis.

## 2.2. Population

The inclusion criteria were:

- non-functional adenoma confirmed by an endocrinological evaluation;
- pituitary MRI included T1 and T2-weighted (axial, sagittal and coronal) before and after gadolinium contrast injection assessed by one senior neuroradiologist (J.L.D.);
- all information was retrieved either from the medical records or by contacting patient's physicians;
- no previous treatment such as radiation therapy or pituitary surgery was performed.

The exclusion criteria were:

- patient younger than 18 years old;
- pregnancy;
- pituitary apoplexy. Acute headaches associated with other acute symptoms such as loss of vision; vomiting; loss of awareness or meningismus were considered as pituitary apoplexy and an exclusion criteria; These acute headaches associated with other neurological symptoms were different from the chronic headache without other symptoms and could be secondary to an adenoma or to another pathology such as migraine and were non-specific;
- one or more missing data;
- functional adenomas.

From 95 consecutive patients, a total of 64 patients were included in this study (Fig. 1).

For each patient, the first pituitary MRI was assessed at the diagnosis. The same senior neuroradiologist (J.L.D.) blinded to patient's previous medical history reviewed all MRI. The size of the adenoma from MRI was divided into micro-adenoma (defined as a pituitary tumor of 1 cm in diameter or less) and macro-adenoma (defined as a pituitary tumor of more than 1 cm in diameter).

The population was prospectively divided into two groups based on MRI results in order to compare the risk factors and evaluate the pituitary function. The group presenting SH on MRI was named the "SH group". The other group was the "control group".

## 2.3. Definition of subclinical haemorrhage

SH was defined by the presence of a haemorrhage or necrosis within the pituitary adenoma confirmed by pituitary MRI without clinical symptoms [1,2]. The features on pituitary MRI were separated into two groups: the presence of blood products inside the pituitary adenoma indicating haemorrhage or haemorrhagic infarction and the presence of pituitary adenoma with no blood. The presence of blood was defined as a lesion with hyperintensity on the T1-weighted images and hypointensity on the T2-weighted images in comparison to the signal of the brainstem (Fig. 2A–D). T2\*-weighted GE MR imaging was able to detect a haemorrhage within the pituitary adenoma for clinical or subclinical haemorrhage [1,2,4,10].

## 2.4. Endocrine evaluation

Endocrine function was evaluated at the diagnosis for each patient by an endocrinologist and all of these adenomas were non-functional. Pituitary deficiency included patients with panhypopituitarism and patients with partial hormonal deficiency (less or equal to two hormonal deficiencies).

## 2.5. Risk factors data

The risk factors obtained from data retrieval were chosen based on factors studied regarding pituitary apoplexy [4,5,7,8,11,12]. Information relative to age, sex, and tumor size were analyzed. Chronic hypertension, diabetes mellitus, malignant disease, and use of anticoagulation or antithrombotic medication and the Cabergoline treatment of patients were evaluated at the diagnosis. All information was obtained from the medical records or by calling the patient's physicians.

## 2.6. Statistical analysis

Using JMP software (version 6.0.3 from SAS Institute Inc.), numeric variables were considered as continuous variables and expressed as means  $\pm$  standard deviation (SD). Inferential statistics were used to study risk factors associated to SH. Normality of the distribution was verified graphically and using the Shapiro-Wilk test ( $P=0.1267$ ) and Kolmogorov-Smirnov test ( $P=0.3140$ ). Qualitative variables were presented as counts and percentages. A value of  $P < 0.05$  indicated statistically significant differences.

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