



**MEDICINA**  
LISBOA

## **DESPACHO 49/2016**

### **Regulamento do Trabalho Final do Mestrado Integrado em Medicina**

Após aprovação do Conselho Científico, em reunião de 19 de julho de 2016, homologo o *Regulamento do Trabalho Final do Mestrado Integrado em Medicina*, anexo ao presente Despacho.

Lisboa, 27 de julho de 2016.

**Prof. Doutor Mamede Alves de Carvalho**  
(Subdiretor da Faculdade de Medicina da Universidade de Lisboa)



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**REGULAMENTO DO TRABALHO FINAL MESTRADO INTEGRADO EM MEDICINA  
FACULDADE DE MEDICINA DA UNIVERSIDADE DE LISBOA (FMUL)**

**ARTIGO 1.º**

**Objetivo**

O presente regulamento estabelece as normas gerais relativas ao Trabalho Final do Mestrado Integrado em Medicina.

**ARTIGO 2.º**

**Âmbito**

A conclusão do Mestrado Integrado em Medicina implica defesa e aprovação no Trabalho Final do Mestrado Integrado em Medicina.

**Artigo 3.º**

**Classificação**

A classificação do Trabalho Final será qualitativa.

**ARTIGO 4.º**

**FASES E PRAZOS**

1. O Trabalho Final pode ser efetuado no 5.º ou 6.º ano do Curso de Medicina.
2. A elaboração do Trabalho Final do Mestrado Integrado em Medicina implica o cumprimento das seguintes fases e prazos:
  - 2.1. O aluno deve entregar a Proposta de Orientador e Unidade Estrutural Associada ao Trabalho Final (Impresso I – anexo I) na Unidade Académica: Gestão do Percurso Académico (UA: GPA) – até ao dia 31 de dezembro, do 6.º ano curricular;
  - 2.2. A Unidade de Gestão Curricular (UGC) envia a Proposta de Orientador e Unidade Estrutural Associada ao Trabalho Final (Impresso I – anexo I) para aprovação por parte do Conselho Científico;

- 
- 2.3. O aluno deve entregar o Impresso II – Júri da Prova Pública – Admissão a Provas (anexo II) em conjunto com o parecer do orientador (Impresso III – anexo III) na UA: GPA – com 15 dias úteis de antecedência relativamente à data de realização da Prova Pública;
  - 2.4. A UGC envia o Impresso II – Júri da Prova Pública – Admissão a Provas e o parecer do orientador (Impresso III) para aprovação por parte do Conselho Científico;
  - 2.5. O aluno deve entregar cópia do Trabalho Final aos membros do júri – com 15 dias úteis de antecedência relativamente à data de realização da Prova Pública;
  - 2.6. A UGC procede à divulgação da Prova Pública – com 5 dias úteis de antecedência;
  - 2.7. A Realização da Prova Pública deve ser efetuada até 31 de julho do 6º Ano curricular;
  - 2.8. Até 5 dias úteis após a discussão pública o aluno deve entregar na UA: GPA:
    - a) A Ata do Trabalho Final do Mestrado Integrado em Medicina (Impresso IV – anexo IV);
    - b) Uma cópia impressa do Trabalho Final;
    - c) A declaração de autorização do depósito do Trabalho Final no Repositório da Universidade de Lisboa (anexo V) e, caso se aplique, declaração de embargo (anexo VI) devidamente assinada pelo orientador.
  - 2.9. O aluno deve enviar uma cópia do Trabalho Final, em formato digital (pdf), via correio eletrónico, para [ggc@medicina.ulisboa.pt](mailto:ggc@medicina.ulisboa.pt) – até 5 dias úteis após a realização da Prova Pública;
  - 2.10. O aluno deve enviar o documento “Ficha de recolha de dados complementares do Trabalho Final do Mestrado Integrado em Medicina” (anexo VII) em formato pdf editável, via correio eletrónico, para [ggc@medicina.ulisboa.pt](mailto:ggc@medicina.ulisboa.pt) – até 5 dias úteis após a realização da Prova Pública.

### **Artigo 5.º**

#### **Definição do Orientador e do Local Associado à Realização do Trabalho Final**

1. O orientador do Trabalho Final pode ser:
  - a) Docente/Tutor da FMUL
  - b) Médico especialista do Centro Hospitalar Lisboa Norte (CHLN) ou Unidades Afiliadas à FMUL
  - c) Investigador do Instituto de Medicina Molecular (IMM)

- 
2. O local de realização do Trabalho Final deverá estar associado a uma unidade estrutural da FMUL: Instituto, Laboratório, Clínica Universitária, Área Disciplinar Autónoma ou Unidade de Investigação Autónoma (consultar Estatutos da Faculdade de Medicina da Universidade de Lisboa).
  3. Sempre que, de acordo com o Orientador, existam dúvidas sobre a Unidade a que ficará afeto o Trabalho Final, a sua definição será efetuada pelo Coordenador do Estágio Clínico.

### **Artigo 6.º**

#### **Modalidades de Trabalho Final Admitidas**

1. O estudante poderá optar por um de dois tipos de trabalho:

*a) Trabalho tipo “artigo científico”*

O trabalho poderá ser em qualquer área de investigação médica, desde investigação básica à investigação clínica. Está incluída nesta última a investigação centrada em casos clínicos, sob a forma de “case report” (exemplo - anexo VIII).

*b) Artigo de revisão*

O artigo de revisão deverá ter uma perspetiva de conceção original na revisão de literatura médica não se limitando à adaptação de um capítulo de livro sobre o tópico (exemplo – anexo IX).

### **Artigo 7.º**

#### **Tema do Trabalho Final**

1. O tema do Trabalho Final será proposto pelo orientador em conjunto com o aluno, carecendo de aprovação pelo Responsável da Unidade ou outro docente doutorado por ele designado.
2. Trabalhos produzidos por alunos em coautoria durante o curso poderão servir de base para o trabalho final por apenas um aluno. Nesta situação o trabalho deverá ser acompanhado por uma declaração assinada pelos restantes coautores autorizando a submissão do trabalho pelo colega para efeitos do trabalho final de mestrado.



## **Artigo 8.º**

### **Constituição do Júri**

1. O Júri é composto por três elementos:
  - a) Presidente do Júri – Professor Responsável da Unidade Estrutural da FMUL a que o orientador está associado ou, em caso de impossibilidade do mesmo, outro docente doutorado por ele designado
  - b) Orientador do trabalho
  - c) Vogal designado pelo Professor Responsável da Unidade, que pode ser:
    - i. Docente/Tutor da FMUL
    - ii. Médico especialista do CHLN ou Unidades Afiliadas à FMUL
    - iii. Investigador do IMM
2. Em casos excecionais e devidamente justificados, o vogal poderá ser um Professor ou Investigador doutorado ou um especialista no domínio do Trabalho Final, exterior ao Centro Académico de Medicina de Lisboa (CAML).

## **Artigo 9.º**

### **Aprovação pelo Conselho Científico**

1. Compete à UGC o envio da Proposta de Orientador e Unidade Estrutural Associada ao Trabalho Final (Impresso I – anexo I) e do Impresso II - Júri da Prova Pública – Admissão a Provas em conjunto com o parecer do orientador (Impresso III) para aprovação por parte do Conselho Científico.
2. O Conselho Científico pode delegar num dos seus membros a aprovação do Orientador e Unidade Estrutural Associada ao Trabalho Final (Impresso II) e do Júri da Prova Pública – Admissão a Provas (Impresso II).

## **Artigo 10.º**

### **Discussão do Trabalho Final – Prova Pública**

1. A divulgação da Prova Pública é efetuada através do Portal da FMUL. Desta divulgação consta a identificação do aluno, o título do Trabalho Final, o local e hora de realização da Prova Pública, bem como a composição do Júri.
2. A Prova Pública realizar-se-á na Unidade Estrutural associada ao Trabalho Final.

3. O aluno disporá de 15 minutos para apresentação oral, seguindo-se a discussão pelos membros do júri (até 45 minutos).
4. No caso do trabalho apresentado ter incorreções/insuficiências, o júri poderá propor a sua revisão, tendo o aluno 30 dias úteis para a apresentar, devendo esta ser novamente discutida em Prova Pública nos 30 dias seguintes.

### Artigo 11.º

#### Regras para a apresentação do Trabalho Final

1. O Trabalho Final do Mestrado Integrado em Medicina deverá ser organizado da seguinte forma:
  - a. **CAPA:** Executar de acordo com modelo em anexo X.
  - b. **1ª PÁGINA:** Cópia da capa, acrescentando o nome do orientador (modelo em anexo XI)
  - c. **2ª PÁGINA:** Resumo em português e inglês (até 300 palavras cada)  
Palavras-chave em português e inglês (até 5).  
No final da página do resumo deve constar a frase “O Trabalho Final exprime a opinião do autor e não da FML”.
  - d. **PÁGINAS SEGUINTE:** Índice.
2. Os Trabalhos Finais devem ser escritos em folhas A4 com intervalos entre linhas de espaço e meio, justificados e em *font Times New Roman*, tamanho 12.
3. A apresentação do Trabalho Final em língua estrangeira carece de autorização do Conselho Científico e, caso exista autorização, este deve ser acompanhado de um resumo em português com, pelo menos, 1200 palavras.

### Artigo 12.º

#### Normas Orientadoras para a Realização do Trabalho Final

1. Especificamente para cada tipo de trabalho:

a) Trabalho tipo “artigo científico”

Estrutura:

Introdução

Material e métodos

Resultados

Discussão

Agradecimentos

Bibliografia

Quadros e figuras (com legendas)

Anexos

Substituído por Caso Clínico na circunstância de se tratar deste tipo de artigo



Notas e esclarecimentos sobre as secções referidas:

- *Introdução*: Deve incluir uma perspetiva e breve revisão da literatura sobre o tema do trabalho
- *Justificação do Trabalho*: especificação dos objetivos originais do trabalho proposto.
- *Material e métodos*: Descrição do material ou da população e métodos utilizados. No caso de caso clínico, os capítulos de material/ métodos e resultados são substituídos pelo capítulo Caso Clínico, sendo a extensão recomendada de 2.000 a 4.000 palavras.
- *Resultados*: Apresentação dos resultados, incluindo o texto descritivo e as tabelas e gráficos correspondentes.
- *Discussão*: Esta deverá incluir a discussão dos resultados e sua contextualização na literatura sobre o assunto, destacando-se a possível originalidade das observações realizadas. As limitações do estudo bem como a sugestão de estudos adicionais e conclusões deverão ser incluídos neste capítulo.  
No caso de caso clínico, a discussão deverá incluir uma revisão da literatura sobre os aspetos do caso clínico que justificam a sua descrição.
- *Bibliografia*: No texto, cada citação bibliografia deve ser indicada no final da frase ou parágrafo a que se refere com um número entre parêntesis referente à ordem de citação. O formato das referências para artigos científicos e para capítulo de livro deverá ser o seguinte:

Artigo Científico: exemplo

Sousa, A. E., Carneiro J., Meier-Schellersheim M., Grossman Z., and Victorino R. M. (2002) CD4 T cell depletion is linked directly to immune activation in the pathogenesis of HIV-1 and HIV-2 but only indirectly to the viral load. *Journal of Immunology* 169:3400-3406.

Capítulo de livro: exemplo

Ahlquist DA. Approach to the patient with occult gastrointestinal bleeding. In: Yamada T. Ed. *Textbook of gastroenterology*. Vol. 1. Philadelphia: JB Lippincott; 1991; 616:33.

- 
- *Quadros e figuras*: Estes poderão ser incluídos nos locais apropriados do texto com respetivas legendas. Alternativamente poderão ser apresentados na forma habitual da submissão de artigo científico, ou seja, com figuras e quadros, um em cada página e uma folha com a legenda das figuras.
  - *Extensão recomendada*: 3.000 a 5.000 palavras.

b) Artigo de revisão

- Introdução: Definição dos objetivos de revisão
- Trabalho de revisão com organização de acordo com opção do estudante/orientador
- Agradecimentos
- Bibliografia
- Quadros e figuras

Estes poderão ser incluídos nos locais apropriados do texto com respetivas legendas. Alternativamente poderão ser apresentados na forma habitual da submissão de artigo científico, ou seja, com figuras e quadros, um em cada página e uma folha com a legenda das figuras.

- Preferencialmente deverá ter as características de uma revisão sistemática (extensão recomendada: 3.000 a 5.000 palavras).

**Artigo 13.º**

**Plágio de Textos**

A deteção de plágio será objeto de procedimento académico disciplinar.

**Artigo 14.º**

**Dúvidas e Casos Omissos**

Todas as dúvidas e casos omissos devem ser apresentados por escrito formalmente na Área Académica.

Anexos:

- Anexo I – Impresso I - Proposta de Orientador e Unidade Estrutural Associada ao Trabalho Final

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- Anexo II – Impresso II - Proposta do Tipo e Tema do Trabalho Final e Júri da Prova Pública – Admissão a Provas
  - Anexo III – Impresso III - Parecer do Orientador
  - Anexo IV – Impresso IV - Ata do Trabalho Final do Mestrado Integrado em Medicina
  - Anexo V – Declaração de autorização do depósito do Trabalho Final no Repositório da Universidade de Lisboa
  - Anexo VI – Declaração de Embargo
  - Anexo VII – Ficha de recolha de dados complementares do Trabalho Final do Mestrado Integrado em Medicina
  - Anexo VIII – Exemplo de trabalho tipo “case report”
  - Anexo IX – Exemplo de artigo de revisão.
  - Anexo X – Modelo de Capa
  - Anexo XI – Modelo de 1.ª página do trabalho final

Aprovação em

Impresso I



Presidente do Conselho Científico  
(Prof. Doutor J. Melo Cristino)

## Proposta de Orientador e Unidade Estrutural Associada ao Trabalho Final

Nome do aluno: \_\_\_\_\_

N.º Aluno: \_\_\_\_\_

Orientador: \_\_\_\_\_

Docente/Tutor da FMUL

Médico especialista do CHLN ou Unidades Afiliadas

Investigador do IMM

Instituto, Laboratório ou Clínica Universitária da FMUL, a que o orientador está associado: \_\_\_\_\_

Professor Responsável da Unidade/docente doutorado por ele designado:

\_\_\_\_\_

**Assinaturas:**

\_\_\_\_\_

Professor Responsável da Unidade/docente  
doutorado por ele designado

Orientador

\_\_\_\_\_

Aluno

Data: \_\_\_\_ / \_\_\_\_ / \_\_\_\_

Presidente do Conselho Científico  
(Prof. Doutor J. Melo Cristino)

**Júri da Prova Pública – Admissão a Provas**

- **Nome do aluno:** \_\_\_\_\_ N.º aluno: \_\_\_\_\_
- **Título do trabalho:** \_\_\_\_\_
- **Tipo de trabalho:**

Investigação básica	<input type="checkbox"/>	Investigação Clínica	<input type="checkbox"/>
Artigo de Revisão	<input type="checkbox"/>	Caso Clínico	<input type="checkbox"/>
- **Trabalho Final redigido em língua:**

Portuguesa	<input type="checkbox"/>	Estrangeira	<input type="checkbox"/>
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- **Instituto, Laboratório ou Clínica Universitária da FMUL:** \_\_\_\_\_
- **Membros do Júri da Prova Pública:**
  - ✓ **Presidente** (Professor Responsável da Unidade/docente doutorado por ele designado):  
\_\_\_\_\_
  - ✓ **Orientador (nome completo):**  
\_\_\_\_\_

Docente/Tutor da FMUL	<input type="checkbox"/>	Médico especialista do CHLN ou Unidades Afiliadas à FMUL	<input type="checkbox"/>
Investigador do IMM	<input type="checkbox"/>		

  - ✓ **Vogal:**  
\_\_\_\_\_

Docente/Tutor da FMUL	<input type="checkbox"/>	Médico especialista do CHLN ou Unidades Afiliadas à FMUL	<input type="checkbox"/>
Investigador do IMM	<input type="checkbox"/>		
- **Data e hora de realização da Prova Pública:**  
\_\_\_\_\_, às \_\_\_\_\_ horas.

**Assinaturas:**

 \_\_\_\_\_  
 Professor Responsável da Unidade/docente  
doutorado por ele designado

 \_\_\_\_\_  
 Orientador

 \_\_\_\_\_  
 Aluno

Data: \_\_\_\_ / \_\_\_\_ / \_\_\_\_

Entregar na Unidade Académia – Gestão do Percurso Académico (piso 01)



LISBOA

UNIVERSIDADE  
DE LISBOA



FACULDADE DE  
MEDICINA  
LISBOA

## PARECER DO ORIENTADOR

Eu, \_\_\_\_\_,  
orientador/a do estudante \_\_\_\_\_  
do Mestrado Integrado em Medicina da Faculdade de Medicina da Universidade de  
Lisboa considero que o Trabalho Final intitulado \_\_\_\_\_  
\_\_\_\_\_ encontra-se suficientemente organizado e estruturado, demonstrando que foram alcançados os objetivos. Mais declara que o referido Trabalho Final se encontra em condições de ser defendido publicamente.

Lisboa, \_\_\_\_\_ de \_\_\_\_\_

\_\_\_\_\_  
Assinatura

### Ata do Trabalho Final do Mestrado Integrado em Medicina

No dia \_\_\_\_\_ do mês de \_\_\_\_\_, no ano de \_\_\_\_\_  
\_\_\_\_\_ pelas \_\_\_\_\_ horas e \_\_\_\_\_  
\_\_\_\_\_ minutos, na Faculdade de Medicina da Universidade de  
Lisboa, teve lugar a prova pública de apreciação do Trabalho Final do Curso de  
Mestrado Integrado em Medicina, apresentada por \_\_\_\_\_

\_\_\_\_\_  
intitulado \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

O Júri foi constituído pelo:

Presidente (Professor Responsável da Unidade) \_\_\_\_\_  
\_\_\_\_\_ ;

Orientador \_\_\_\_\_  
\_\_\_\_\_ ;

Vogal \_\_\_\_\_  
\_\_\_\_\_ ;

Finda a prova o Júri reuniu de imediato para deliberar sobre o resultado final:

Recusado

Aprovado

Fundamentação: \_\_\_\_\_  
\_\_\_\_\_

Presidente:

Orientador:

Vogal:

Aluno:

## DECLARAÇÃO

Nome: \_\_\_\_\_

Correio electrónico: \_\_\_\_\_ Telefone: \_\_\_\_\_

Número do Bilhete de Identidade: \_\_\_\_\_ Mestrado  Doutoramento

Título dissertação / tese \_\_\_\_\_

Orientador(es): \_\_\_\_\_

Ano de conclusão: \_\_\_\_\_ Faculdade / Instituto: \_\_\_\_\_

Designação do Mestrado ou do Ramo de Conhecimento do Doutoramento:  
\_\_\_\_\_

Declaro sob compromisso de honra que a tese/dissertação agora entregue corresponde à versão final apresentada ao júri.

Declaro que concedo à Universidade de Lisboa e aos seus agentes uma licença não-exclusiva para arquivar e tornar acessível, nomeadamente através do seu repositório institucional, nas condições abaixo indicadas, a minha tese ou dissertação, no todo ou em parte, em suporte digital.

Declaro que autorizo a Universidade de Lisboa a arquivar e, sem alterar o conteúdo, converter a tese ou dissertação entregue, para qualquer formato de ficheiro, meio ou suporte, nomeadamente através da sua digitalização, para efeitos de preservação e acesso.

Concordo que a minha tese ou dissertação seja colocada no Repositório da Universidade de Lisboa com o seguinte estatuto (assinale apenas uma das hipóteses):

1.  Disponibilização imediata do conjunto do trabalho para acesso mundial;
2.  Disponibilização do conjunto do trabalho para acesso exclusivo na Universidade de Lisboa durante o período de  1 ano,  2 anos ou  3 anos, sendo que após o tempo assinalado autorizo o acesso mundial (anexo justificação do embargo devidamente assinada pelo orientador);
3.  Disponibilização apenas dos metadados descritivos (autor, título e resumo, entre outros) sendo que anexo justificação da não disponibilização do texto integral, assinada pelo orientador);

Retenho todos os direitos de autor relativos à tese ou dissertação, e o direito de a usar em trabalhos futuros.

Lisboa, \_\_\_\_ / \_\_\_\_ / \_\_\_\_

Assinatura: \_\_\_\_\_



## DECLARAÇÃO

*Na qualidade de orientador(a) do Trabalho Final do Mestrado Integrado em Medicina da*

*Faculdade de Medicina de Lisboa do(a) aluno(a) \_\_\_\_\_*

*\_\_\_\_\_ declaro que o seu trabalho intitulado \_\_\_\_\_*

*\_\_\_\_\_ deverá ter o seguinte estatuto:*

Disponibilização do conjunto do trabalho para acesso exclusivo na Universidade de Lisboa durante o período de  1 ano,  2 anos ou  3 anos, sendo que após o tempo assinalado autorizo o acesso;

Disponibilização apenas dos metadados descritivos (autor, título e resumo, entre outros);

*Justificação do embargo: \_\_\_\_\_*

\_\_\_\_\_

Lisboa, \_\_\_\_\_

Assinatura do Orientador(a):

**FICHA DE RECOLHA DE DADOS COMPLEMENTARES**  
**TRABALHO FINAL DO MESTRADO INTEGRADO EM MEDICINA**

**Ano Letivo**

A necessidade de recolha dos dados em baixo identificados resulta da obrigatoriedade de registo de atribuição do grau no RENATES - Registo Nacional de Teses e Dissertações e do facto de nesta base de dados serem solicitados elementos que não estão previstos nas normas do Trabalho Final em vigor.

**Dados de Identificação do aluno:**

Nome do Aluno: \_\_\_\_\_

\_\_\_\_\_

Nº do 6º Ano: \_\_\_\_\_, Nº da FMUL: \_\_\_\_\_

Título do Trabalho: \_\_\_\_\_

\_\_\_\_\_

**Dados complementares referentes ao orientador:**

NOME COMPLETO DO ORIENTADOR: \_\_\_\_\_

\_\_\_\_\_

Nº de Identificação: \_\_\_\_\_

Tipo de Identificação: \_\_\_\_\_

**Dados complementares referentes ao Trabalho Final:**

Área disciplinar do Trabalho Final: \_\_\_\_\_

Palavras-Chave (cerca de 5 em português e em inglês):

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

## Fou Rire Prodromique

### Case Report and Systematic Review of the Literature

Miguel Coelho, José M. Ferro

Stroke Unit, Department of Neurology, Hospital Santa Maria, Lisboa, Portugal

*Fou rire prodromique* is a rare behavioral abnormality characterized by prolonged burst of uncontrolled laughter preceding the onset of an acute neurological deficit [1-3].

#### Case Report

A 51-year-old hypertensive woman, with a history of previous left dorsal midbrain hematoma and multiple cavernomas identified by MRI, was admitted because of a speech disorder and right-sided weakness, preceded by an uncontrolled fit of laughter. The laughter was of abrupt onset and inappropriate to the situation, and the patient could not stop it voluntarily. Throughout the episode the patient was always able to establish contact with her husband. The laughter lasted 30 min and ended abruptly, and was followed in seconds by the onset of a speech disorder and right-sided weakness. The husband described the patient as a strict and emotionally stable person prior to this event.

On admission, the patient was drowsy, dysarthric, with a non-fluent aphasia and a right-sided hemiparesis. There was a residual left Horner syndrome and left limb ataxia from the previous brainstem hematoma. The patient was continuously whimpering. Cranial CT scan (fig. 1) revealed a left hematoma involving the anterior part of the thalamus and the internal capsule.

On following days, drowsiness, dysarthria, aphasia and motor deficit improved. The patient kept whimpering continuously and was abulic. Two months later, she was improved but had a residual right motor deficit. Pathological laughter did not recur. MRI de-

icted a resolving hematoma in the left thalamus, an old left dorsal midbrain hemorrhage, periventricular white matter changes, and two cavernous angiomas localized to the head of right caudate nucleus and right temporal lobe (fig. 2). We plotted the thalamic hematoma on a horizontal section of thalamic nuclei [4]. For this purpose, a bidimensional atlas of the thalamus [4] and co-planar coordinates were used. The lesion was localized to the internal ventro-oral, ventrointermedial, intralamellary, external ventro-oral and median nuclei of the left thalamus (fig. 3).

#### Systematic Review of Previously Reported Cases

##### Review Method and Conduction

A literature search was based on: (i) a Medline search using the key words 'fou rire prodromique', 'pathological laughter', 'pathological mirth' and 'gelastic seizure'; (ii) a hand search of references of published cases/case series; (iii) a hand search on textbooks of neurology, epilepsy and cerebrovascular diseases. Excluded from this review were non-prodromal cases of pathological laughter and cases of gelastic seizures. Also excluded were papers written in languages other than English, Portuguese, French, Spanish or Italian.

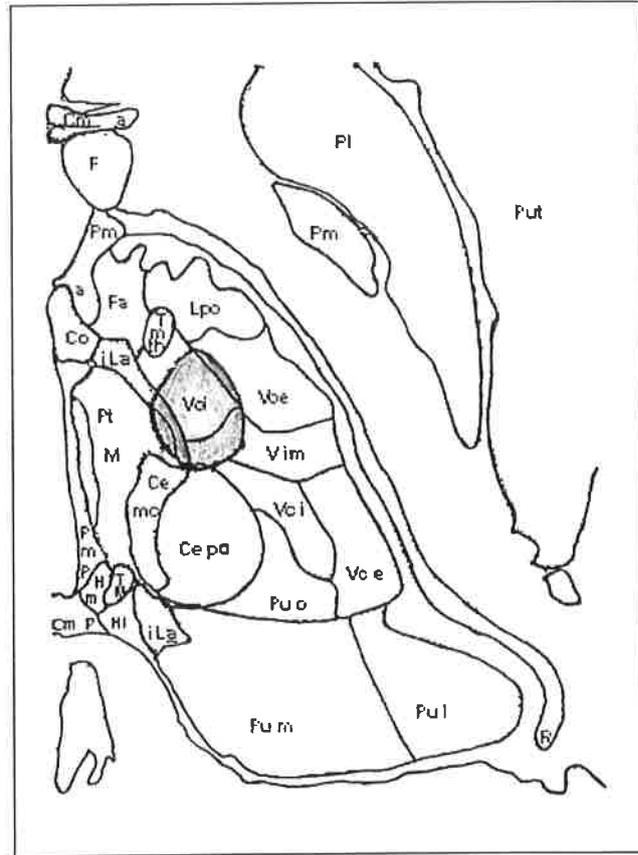
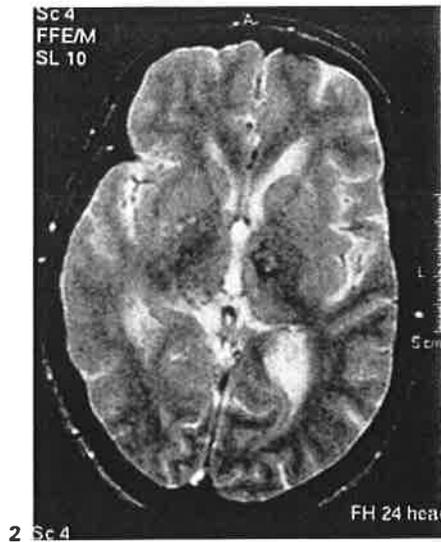
For each case report, the following data was extracted: gender, age and history of previous stroke; duration of laughter and latency to neurological deficit; other behavioral disturbances; results of neuroimaging and/or autopsy; recurrence of laughter.

##### Review Results

We found 18 published cases of *fou rire prodromique* (table 1), including thirteen strokes [1, 3, 5-15] (one haemorrhagic [5]). Pontine infarcts were found in five patients [3, 6, 8, 9, 15], but cortical [10, 11, 16] and sub-cortical [1, 7, 13] lesions are also reported. In four patients [6, 9, 12, 15] the *fou rire* relapsed. Behavioral distur-



**Fig. 1.** CT scan. Hematoma in the anterior part of the left thalamus and the left internal capsule.



**Fig. 2.** MRI. Hematoma in the left thalamus and two cavernous angiomas in the right caudate nucleus and right temporal lobe.  
**Fig. 3.** Hematoma plotted on a horizontal section of thalamic nuclei, 2.7 mm superior to anterior commissure–posterior commissure line. M = Median nucleus; iLa = intralamellar nucleus; Voi = internal ventro-oral nucleus; Voe = external ventro-oral nucleus; Vim = ventrointermediate nucleus; CePc = central parvocellular nucleus; Cm a = anterior commissure; Cm P = posterior commissure; Pu m = medial pulvinar nucleus; Pu l = lateral pulvinar nucleus.

**Table 1.** Case reports of fou rire prodromique

Case reports (n = 18)	Gender	Age	History of past stroke	Duration of laughter	Latency to neurological deficit	Autopsy	Neuroimaging	Other brain lesions	Pathological crying/laughter or other behavioral disturbance	Recurrence
Féré [17] 1903	M	64	no	n.a.	4 months	no	n.a.	n.a.	memory deficit; decrease intelligence; somnolence	no
Andersen [5] 1936	F	58	previous pseudo-bulbar palsy	1½ h	immediate	bilateral thalamic, capsular and lenticular hemorrhage with intraventricular blood, originating from posterior communicating artery	n.a.	n.a.	no	n.a.
Martin [12] 1950	M	25	no	n.a.	n.a.	large basilar aneurism	n.a.	n.a.	no	two episodes previous to neurological deficit
	F	25	no	n.a. (<24 h)	2 months	no	n.a.	n.a.	no	no

**Table 1** (continued)

Case reports (n = 18)	Gender	Age	History of past stroke	Duration of laughter	Latency to neurological deficit	Autopsy	Neuroimaging	Other brain lesions	Pathological crying/laughter or other behavioral disturbance	Recurrence
Swash [14] 1972	F	45	no	3 h	n.a.	no	Scan Tc 99m: increased uptake in lateral, anterior and inferior aspects of left temporal lobe	no	pathological laughter; aphasia; mumbling voice; neologisms; neglect; perseveration of speech and gestures	no
Walli [3] 1993	F	35	no	15 min	15 min	no (patient died)	MRI: bilateral symmetrical infarct of basis pontis, mainly left half	no	no	no
Ceccaldi [1] 1994	F	47	no	15 min	few min	no	MRI: posterior part of left parahippocampal gyrus, left posterolateral thalamus and adjacent part of internal capsule	no	no	no
Ceccaldi [16] 1995	F	57	no	10–15 min	3 episodes before deficit; 24 h between last episode and deficit	no	MRI: right prerolandiic tumor	no	no	no
Ertekin [9] 1997	M	57	no	60 min	n.a.	no	MRI: left pontine infarct	no	pathological crying and laughing	few times in first 3 days after stroke; one year later with infarct at head of caudate nuclei
	M	67	no	60 min	n.a.	no	MRI: normal	no	pathological crying and laughing	no
	F	85	no	15 min	n.a.	no	CT: normal; MRI not possible to perform	no	no	no
Tei [15] 1997	F	69	n.a.	15–30 s	n.a.	no	MRI: ventromedial pontine infarct	no	no	several spells during 3 weeks
Lago [11] 1997	M	78	no	15 min	n.a.	no	CT: infarct in posterior territory of left MCA	sub-acute infarct of posterior branches of right MCA	agitation	no
Carel [7] 1997	M	61	n.a.	2 min	immediate	no	MRI: left infarct in lenticular nuclei, caudate nuclei and anterior insula	no	no	no
Assal [6] 2000	F	61	no	approximately 12 h	n.a.	no	MRI: infarction in right ventral pons	no	mild attentional deficit and decreased phonological fluency	several spells during a week
Garg [10] 2000	F	50	no	15 min	immediate	no	CT: cortical infarct in the territory of superior division of left MCA	no	no	no
Couderq [8] 2000	M	49	yes (right MCA stroke; no sequela)	15 min	immediate	no	CT: infarct in left pons; spontaneous hyperdensity in basilar artery	old infarct in superficial territory of right ACM	time and place disorientation; visual and auditory hallucinations without insight	no
Osseby [13] 1999	M	12	no	1 min	immediate	no	MRI: infarction of left lenticular nucleus, left insula and mild involvement of left internal capsule	no	simultaneous pathological crying; aphasia; occasional pathological laughter	no

n.a. = Not available; MCA = middle cerebral artery.

bances were present in nine patients [6, 8, 9, 11, 13–15, 17]. In one patient [13], there was simultaneously a pathological fit of laughter and crying preceding the neurological deficit. In another two [9] patients, typical spasmodic laughter and crying developed a few days after the onset of stroke. In the reported cases, *fou rire* usually lasts between a few seconds to several hours (table 1). The latency between its ending and the start of neurological deficit varies widely, between milliseconds to months (table 1).

#### Discussion

When preceding the onset of an acute neurological deficit, pathological laughter is named *fou rire prodromique* [2, 3, 11, 15], as first reported by Féré in 1903 [7]. In some reported cases [12, 17], the neurological deficit started more than 24 h after the *fou rire*. In these cases, it is not appropriate to describe the *fou rire* as prodromique. The reports of one patient [13] with *prodromique* laughter and crying, and of another two patients [9] with pathological crying and laughter following the *fou rire*, suggest that *fou rire* and spasmodic laughter may share common physiopathology [9]. In the case we report, *fou rire* was followed by prolonged continuous whimpering. Although an EEG could not be performed during the episode of laughter, the duration of the laughter (much longer than the usual 30 s of gelastic seizure), the persistence of consciousness and the lack of automatisms are not in favor of a gelastic seizure [2, 11, 16].

Wilson [18] proposed the existence of a supranuclear pontobulbar facio-respiratory center for the control of laughter, connecting the facial nucleus in the pons with that of the tenth nerve in the medulla and the phrenic nerve in the upper cervical cord. An integrative center has been proposed, located in the medial thalamus, hypothalamus and subthalamus. This center would be under the voluntary control of bilateral corticobulbar tract and involuntary control of bilateral orbitofrontobulbar respiratory tract. The orbitofrontobulbar would inhibit the corticobulbar one. A lesion in any of these tracts or centers would deregulate the system and provoke pathological laughter. This is in accordance with the various locations of lesions causing pathological laughter. A recent alternative hypothesis [19], claiming a role of a lesion of the cerebro-ponto-cerebellar pathways for pathological laugh and crying is also compatible with the various distributions of lesions that we found in the systematic review. Gelastic seizures elicited by electric stimulation [20] suggest the involvement of the anterior cingulate gyrus in the motor act of laughter. Subthalamic nucleus stimulation for Parkinson's disease induced mirthful laughter in two patients [21]. The authors ascribed this effect to damage to the limbic portion of the subthalamic nucleus and its interconnections to the basal ganglia and thalamus, or, alternatively, to electric current diffusion to neighboring structures such as the hypothalamus.

In our case, the origin of *fou rire prodromique* may be due to the interruption of efferent pathways from the medial, intralaminar and ventrolateral formations of the thalamus [20] to the anterior cingulate gyrus [22]. The medial thalamic lesion may cause prolonged and inappropriate laughing by disrupting integration of the cognitive and emotional clues that trigger laugh in adequate social context. The lesion responsible for the *fou rire* must be smaller than the hematoma depicted on CT, because the *fou rire* ended before the start of motor deficit, being substituted by continuous whimpering. However, the presence of a previous hematoma, multiple cavernomas and subcortical white matter lesions make inferences on the anatomical interpretation of *fou rire* difficult in this case. The presence of the other vascular lesions localized to the left dorsal midbrain, head of right caudate nucleus and right temporal lobe, in combination with the

thalamic hemorrhage could be the trigger of the *fou rire*. Finally, other hypothesis should be considered, such as the thalamic hematoma causing ephaptic excitation of the internal capsule or disinhibition of neighboring structures.

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## Update on subarachnoid haemorrhage

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becoming effective alternatives to surgical treatment, SAH should turn out to be of interest to neurologists, in particular to those devoted to stroke, emergency and neurointensive care. Despite stable incidence, the mortality of SAH has decreased in the last two decades due to better neurosurgical techniques and neurocritical care and to advances in interventional neuroradiological procedures.

We review the recent advances in the clinical and diagnostic aspects of SAH and in the genetics of intracranial aneurysms. A systematic review of the treatment of SAH and grading of the available evidence is included.

**Key words** subarachnoid haemorrhage · intracranial aneurysm · vasospasm

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**Abstract** Subarachnoid haemorrhage (SAH) is less frequent than ischaemic stroke or intracerebral haemorrhage, but has a high public health relevance because it can affect young and middle-age adults, has considerable mortality and morbidity, it is treatable and preventable. SAH is traditionally a topic for neurosurgeons. However as endovascular interventions are

### Abbreviations

SAH	subarachnoid haemorrhage
RR	relative risk
OR	odds ratio
CT	computerized tomography
CSF	cerebrospinal fluid
MR	magnetic resonance
EEG	electroencephalogram
ECG	electrocardiogram
WFNSS	World Federation of Neurological Surgeons Scale

RCT	randomised controlled trial
ICU	intensive care unit

### Introduction

In this review, we have included selected advances in the clinical and diagnostic aspects of SAH and a systematic review of the treatment of ruptured intracranial aneurysms, SAH and its complications that we judge to be relevant to the general neurologist or to those with an interest in stroke care. Since 2000 other reviews [1, 8, 55, 102, 104] on SAH and cerebral aneurysms have been

published. SAH represent only 5% of all strokes, but it is responsible for 25% of all fatalities related to stroke. SAH is more common in females (3:2). SAH is an emergency. Patients with SAH should be referred urgently to a tertiary care centre providing expert cerebral aneurysm treatment, including endovascular, neurosurgical and neurointensive care management [92].

### SAH as a cause of death

SAH is a serious condition: global mortality ranges from 32–67% [32]. 20 to 30% of the survivors are left with disabling sequelae. Less than 1/3 of the patients regain their previous occupation and life style. Among those who reach a tertiary care centre, 1/4 will die from complications of SAH (mainly vasospasm) or its treatment within 2 weeks. SAH is also a cause of sudden death. Around 20% of SAH patients die before arriving at the hospital. The estimated risk is 12% for aneurysmal SAH and 45% for posterior circulation aneurysms [35]. Sudden death may be due to cardiac arrhythmias or to global cerebral ischaemia and oedema secondary to the sudden rise of intracranial pressure due to intracranial bleeding from a large arterial source.

### Epidemiology of SAH

Contrary to other stroke types, the incidence of SAH remains stable: ~10/100000/year (6 to 16) [50]. The most recent epidemiological studies showed that contrary to the traditional concept, the incidence of SAH increases with age [91]. The occurrence of SAH exhibits a seasonal (winter and spring), diurnal (late morning) and daily (Sunday) peak pattern [25].

### Risk factors for SAH

The risk factors for SAH are not exactly the same as for other types of stroke. The most important vascular risk factors for SAH are hypertension, smoking and high alcohol intake [90]. Feigin et al. [26] recently updated their previous systematic review of risk factors for SAH, using data from population-based and case-control studies and confirmed that hypertension (RR longitudinal studies 2.5, OR case-control studies 2.6), smoking – RR longitudinal studies 2.2, OR case-control studies 3.1) and excessive alcohol consumption (RR longitudinal studies 2.1, case-control studies 1.5) were risk factors for SAH. Non-white ethnicity was a less robust risk factor, while oral contraceptives had no effect and hormonal replacement therapy, high cholesterol and diabetes were protective factors for SAH. Smoking and hypertension were also the more important risk factors for SAH in Asian-

Pacific cohorts [23]. "Binge" alcohol intake was a risk factor for SAH in some studies performed in Scandinavia but not in Asia. Unfortunately, more than 1/3 of smokers continue to smoke after surviving a SAH, in particular those who started their habit at a young age, and those with history of depression and alcohol abuse [4].

The ACROSS study confirmed moderate to extreme physical exertion as a trigger of SAH (but not heavy smoking or binge drinking) [3].

### Genetics of SAH and intracranial aneurysms

First degree relatives but not second degree relatives of SAH patients have an increased risk of SAH [80]. In the population based study performed in Scotland, the 10-year prospective risk was 1.2 for first degree relatives and 0.5 for second degree relatives. The risk was highest in families with 2 first degree relatives affected [89].

An exceedingly small percentage of aneurysmal SAH is due to rare monozygotic disorders with Mendelian inheritance. These include primary connective tissue diseases (Ehlers-Danlos – mutation in collagen type 3; Marfan's syndrome – mutations in fibrillin-1 gene; pseudoxanthoma elasticum – mutations in *ABCC6* gene), neurofibromatosis type 1 and polycystic kidney disease (mutations in *PKD1* and *PKD2*).

Other evidence for a genetic predisposition to SAH and intracranial aneurysms comes from association studies. Candidate genes included *ELN* and *COL1A2* that code structural proteins of the extracellular matrix and ACE II polymorphisms [78, 87]. In genome-wide screen linkage studies, the following susceptibility genes and loci have been identified: chromosome 7q11, 14q22 and 5q22–31 in Japanese families, chromosome 19q13.3 in Finnish families, chromosome 2p13 in Dutch families, chromosome 1p34.3–36.13 in US families.

Other studies associated some genes with SAH prognosis. ApoE – E4 was associated with worse prognosis but no association was found in other studies; eNOS – 786TC was associated with increased susceptibility to vasospasm; PAI-1-4g was associated with worse prognosis.

For recent reviews on this topic see [58, 95, 105].

### Clinical aspects of SAH

SAH produces a rather typical clinical picture: a sudden onset, very severe headache, occurring during activity, followed in some cases by a transient disturbance of consciousness or vomiting. Neck stiffness and other meningeal signs are the main findings in the physical exam. Fundoscopy may reveal a retinal, subhyaloid or vitreous haemorrhage (Terson's syndrome) [56]. Less

commonly, SAH produces motor defects, aphasia, seizures, ptosis, diplopia or a complete III nerve palsy (Posterior Communicating Artery Aneurysm), visual troubles (carotid aneurysms) and amnesia (Anterior Communicating Artery Aneurysm)

However, about 20% of SAH cases are not recognised in their first medical encounter [21, 49]. Most common misdiagnosis is migraine, tension headache and headache related to high blood pressure. The difficulty arises from the fact that sudden onset headache is a common condition that is sometimes due to SAH or other serious condition but is mostly harmless. Landtblom et al. [47] performed a prospective study of 137 patients with sudden onset headache of thunderclap type and only 11% had a SAH. Differential diagnosis of sudden onset headache is described in Table 1.

SAH is preceded in about 10% of the cases by a "sentinel headache" or warning leak, an episode of headache similar to that of SAH, and preceding it by days or weeks. This is currently judged to be in fact a minor undiagnosed SAH. A recent systematic review concluded that their true incidence may vary from 0 to 40%, depending on the rate of misdiagnosis in the community. Sentinel headache is more common in aneurysmal than in non-aneurysmal SAH, indicating that the majority of sentinel headaches are not due to recall bias [72].

Bleeding in the spinal subarachnoid space (Fig. 1), originating from a spinal source or from diffusion from an encephalic source, can produce radicular pain mimicking sciatica, back pain [44] or a "coup de poignard" syndrome, a sudden precordial pain simulating myocardial infarction or aortic dissection [5, 13].

SAH can also present as a psychiatric condition: a burst of aggressive or bizarre behaviour [73] or as delirium. Psychiatric manifestations are common in the acute phase: depression - 60%, denial - 28%, apathy -

**Table 1** Differential diagnosis of sudden onset headache

Primary thunderclap headache
Primary exertional headache
Primary headache associated with sexual activity
Primary cough headache
Sudden onset migraine
Cervicogenic headache
Headache related to cerebrovascular disorders
Subarachnoid haemorrhage
Intracerebral haemorrhage
Ischaemic stroke
Carotid or vertebral dissection
Dural sinus thrombosis
Hypophyseal apoplexy
Intracranial neoplasms and cysts
Acute meningitis
Sinusitis



**Fig. 1** Spontaneous spinal subarachnoid haemorrhage. MR (T<sub>1</sub> sequence) of the dorsal and lumbar spine showing hematic hyperintensities anterior to the spinal cord

28% and delirium - 18% [12]. Delirium is more frequent in patients with intraventricular bleeding, hydrocephalus and baso-frontal haematomas, reflecting the involvement of anatomical networks subserving sustained attention, declarative memory and the expression of emotional behaviour [11].

SAH in the elderly has some distinct clinical aspects: a larger proportion of elderly patients present in poor clinical condition. Complications, both medical and neurological, in particular hydrocephalus, are more common. The prognosis is worse than in younger patients. Half of the patients die and only 1 out of 6 SAH patients older than 75 will leave the hospital alive and independent [33, 67].

## Diagnosis of SAH

### Is lumbar puncture still necessary?

Subarachnoid haematic densities on an early brain CT are diagnostic of SAH. However if the amount of blood in the CSF is minute it may not be detected by CT. Sensitivity of new generation CTs ranges from 93 to 100% [55]. The later the CT is performed, the lower the likelihood of having hyperintensities in the subarachnoid

space, because they will become gradually isodense. 30% of the scans will be negative within 4 days and 50% at one week after the initial bleeding.

In suspected cases with negative scans a lumbar puncture must be performed. Xanthochromia in CSF is due to bilirubin (from haemoglobin) and is diagnostic. Xanthochromia develops between 2 to 12 h after bleeding and takes at least 2 weeks to clear. Traumatic lumbar puncture (about 20%) causes bloody CSF (decreasing in successive samples) but not xanthochromia (if centrifugation is not too delayed). Spectrophotometry of the CSF is the recommended method of analysis. This should be done on the final bottle of CSF collected [6]. Fig. 2 shows a proposed flow chart for the diagnosis of SAH.

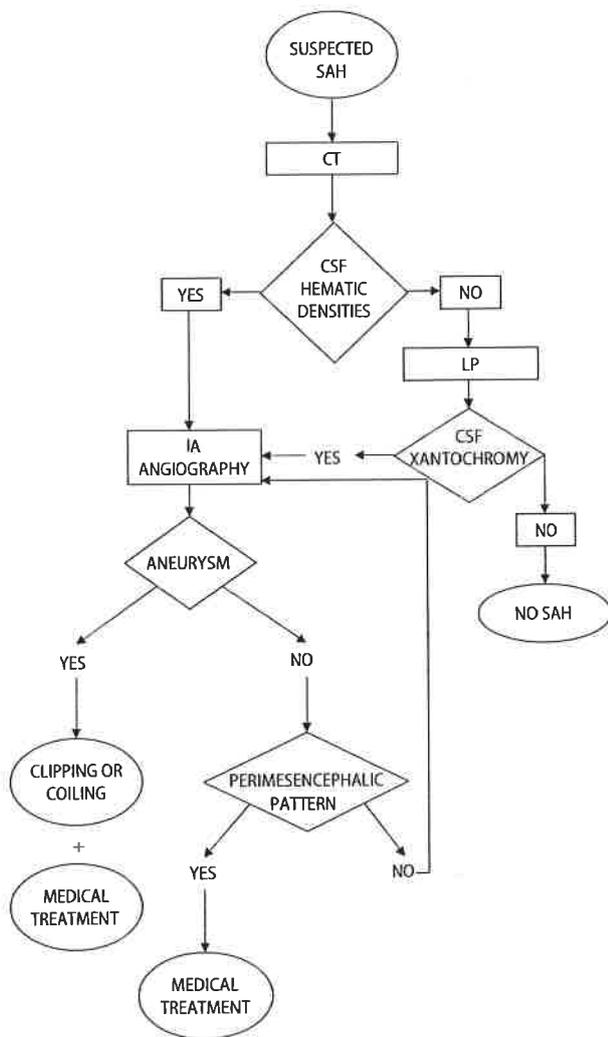


Fig. 2 Flow chart for the diagnosis of SAH

## MR, CT or intra-arterial angiography?

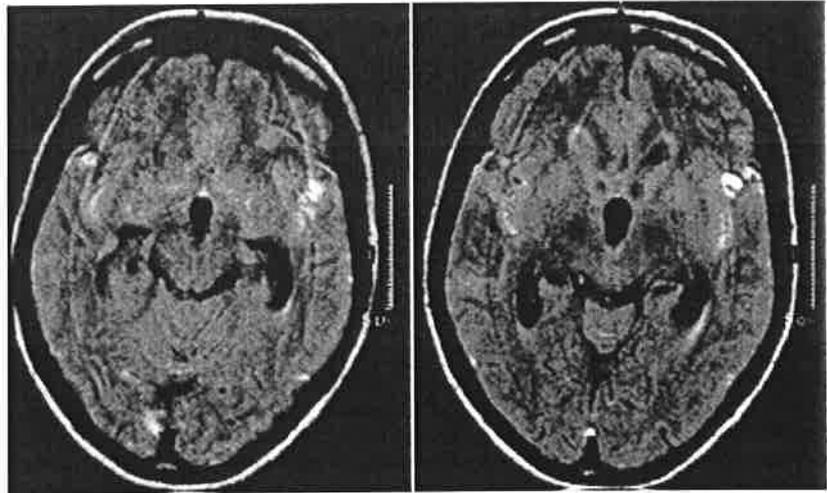
MR can also be useful to detect cases with delayed presentation, by showing hyperintensity signals in the subarachnoid space (Fig. 3) [46, 60]. Intra-arterial angiography remains the gold standard for the diagnosis of aneurysms and should be performed as soon as possible, to hasten endovascular or surgical treatment of the aneurysm to prevent rebleeding (Fig. 4). Although it can detect aneurysm as small as 3 mm, MR angiography is not as sensitive as intra-arterial angiography and produces false positive results. In some cases (e.g. elderly patients or patients with severe limb or aortic atheroma) or in some institutions, CT angiography is used instead of intra-arterial angiography. However the sensitivity of CTA compared to intra-arterial angiography varies between 85 and 98%.

## Etiology of SAH

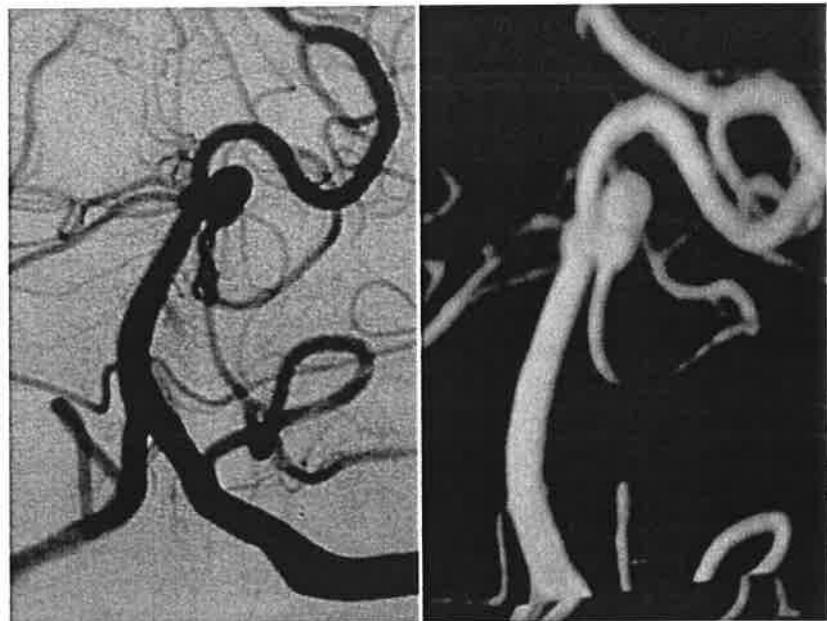
About  $\frac{3}{4}$  of the cases of SAH are due to ruptured intracranial aneurysms. Other causes are cranio-cerebral trauma, arterio-venous malformations, dural fistulae, dural sinus thrombosis, intracranial arterial dissection, mycotic aneurysms, bleeding diseases and drugs (cocaine) [34]. The majority of these causes can be identified by clinical history and MR. In about 20% of the cases no cause is found. Angiography must be repeated in such patients in a variable interval (days to 2 weeks) after the first one, but the yield of repeat angiography is very low (~2%). In a few patients, hematic densities are limited to the perimesencephalic cisterns, with no blood on the convexity, the interhemispheric fissure or the vertical part of the Sylvian fissure (Fig. 5). These patients have a perimesencephalic pattern of SAH [103] that is rarely due to aneurysmal rupture (<10%). It is considered to be of venous origin or due to intramural dissection. This pattern only applies to patients with early (<4 days) scans. Perimesencephalic SAH has a benign course although it can be complicated by hydrocephalus. In one case-series, the presence of intraventricular blood was associated with the development of acute hydrocephalus, a higher complication rate and a poorer outcome in comparison with patients without intraventricular blood [27]. In patients with perimesencephalic SAH repeat angiography is not warranted if the first angio is negative.

There are multiple aneurysms in about 25% of the cases. Patients with multiple aneurysms are younger than those with single aneurysms, pointing towards a stronger genetic component.

**Fig. 3** MR hyperintensities in the Sylvian and calcarine fissures in a patient with subarachnoid bleeding a week before



**Fig. 4** Intra-arterial angiography. 2-D (left) and 3D (right) views of a basilar aneurysm



## Complications of SAH

The clinical course of SAH can have several complications. The most important neurological complications are rebleeding [65], intracerebral haematoma and intraventricular haemorrhage, vasospasm, hydrocephalus and seizures. Continuous EEG monitoring may detect non-convulsive status epilepticus in about 8% of SAH patients and unexplained coma or neurological deterioration [19].

### ■ Rebleeding

Rebleeding is the most feared complication and peaks in the first few days after the first bleeding. Rebleeding is more frequent in patients with poor clinical condition and in those with large aneurysms. Rebleeding carries a dismal outcome. If the aneurysm is not treated, the risk of rebleeding within 4 weeks is estimated to be of 35–40% [31]. After the first month the risk decreases gradually from 1–2%/day to 3%/year [111].

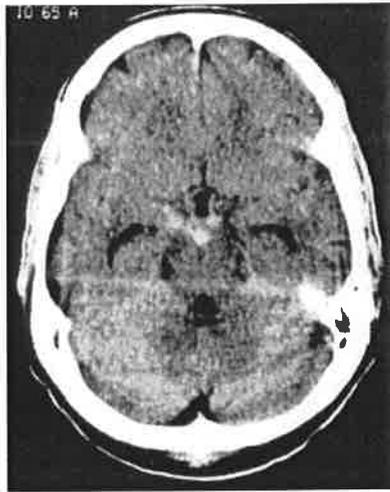


Fig. 5 Acute cranial CT of a patient with a perimesencephalic pattern of SAH

### Cardiac complications of SAH

ECG changes are common in acute SAH, being present in about  $\frac{3}{4}$  of acute SAH patients and include: sinus bradycardia or tachycardia, QT prolongation, bundle branch block, ST depression or elevation, T wave changes and pathological Q waves. Some of these changes may mimic those of acute myocardial infarction [42, 54, 79]. In addition, enzyme elevation, echocardiogram wall motion abnormalities, abnormal thallium scans, pulmonary oedema and myocardial pathological changes at autopsy have been reported. These cardiac changes are thought to be mediated through systemic release of adrenaline and noradrenaline and through sympathetic and parasympathetic cardiac nervous connections. As mentioned in the introduction, SAH can cause cardiac arrest and sudden death. Most cases of cardiac arrest occur at the time of initial or recurrent SAH. Resuscitation is worthwhile as it is often successful and the outcome of survivors is not worse than that of other SAH patients [96].

### Diagnosis of vasospasm

Transcranial Doppler is used for diagnosis of vasospasm in SAH patients. Compared to angiography, for the middle cerebral artery, transcranial Doppler has a high specificity (99%) and high positive predictive (97%) values. However the sensitivity is moderate (67%); for the anterior cerebral artery specificity is 76% and sensitivity is 42%; for the other arteries there is lack of evidence of accuracy of transcranial Doppler [53].

### Prognosis of SAH

The major prognostic factor in SAH is the severity of the initial bleeding, measured either clinically by grading scales such as the Glasgow Coma Scale, Hunt and Hess or the WFNS scales (Table 2) and from the amount of haematic densities in the admission scan, measured by the Fisher's or the Hidja's scales (Table 2) [76]. Other variables with influence in prognosis are age, intracerebral and intraventricular haemorrhage, blood pressure values, location [16] and size of the aneurysm and time to diagnosis.

Long-term neuropsychological consequences (memory and executive deficits) are well known among SAH survivors. Less known is neuroendocrinal dysfunction [45] showed pituitary deficiency in 18 of 40 SAH survivors. Many patients who survive an episode of SAH have disorders of sleep and wake, which are related to their quality of life [81].

Epilepsy occurs in 7–12% of SAH survivors and it is predicted by cerebral infarction and subdural

Table 2 Commonly used clinical and imaging SAH scales

#### World Federation of Neurological Surgeons grading system

WFNS grade	Glasgow Coma Scale Score	Focal deficit
I	15	Absent
II	14–13	Absent
III	14–13	Present
IV	12–7	Present or absent
V	6–3	Present or absent

#### Hunt and Hess grading system

Category*	Criteria
Grade I	Asymptomatic or minimal headache and slight nuchal rigidity
Grade II	Moderate to severe headache, nuchal rigidity, no neurologic deficit other than cranial nerve palsy
Grade III	Drowsiness, confusion, or mild focal deficit
Grade IV	Stupor, moderate to severe hemiparesis, possible early decerebrate rigidity and vegetative disturbances
Grade V	Deep coma, decerebrate rigidity, moribund appearance

\* Serious systemic disease, such as hypertension, diabetes, severe arteriosclerosis, chronic pulmonary disease, and severe vasospasm seen on arteriography result in placement of the patient in the next less favourable category

#### Fisher scale

Group 1: No detectable blood on CT
Group 2: Diffuse blood that does not appear dense enough to represent a large, thick homogenous clot.
Group 3: Dense collection of blood that appears to represent a clot greater than 1 mm thick in the vertical plane or greater than 5x3 mm in longitudinal and transverse dimensions in the horizontal plane; severe spasm predicted.
Group 4: Intracerebral or intraventricular clots, but with only diffuse blood or no blood in basal cisterns.

haematoma and is associated with poor functional recovery and quality of life [15]. Seizures are infrequent in cases treated only with coil embolization [10].

### Treatment: a review of the evidence

We performed a literature review for each of the therapeutic interventions listed below in the Medline, Cochrane Library, Neurosurgical and Neurological Intensive Care books. Priority was given to randomised controlled trials, meta-analyses and systematic reviews. If lacking, data provided by other clinical trials and expert opinions were considered. The level of evidence was classified according to Brainin et al. [7].

The search strategy was planned using the key words: aneurysm\*, subarachnoid, haemorrhage (or hemorrhage). For each of the treatments and intervention other key words were specifically used (e.g. surgery OR surgical OR clipping OR neurosurg\* endovascular OR coil\* OR "interventional neuroradiology" OR catheter\* OR neurovascular). Tables 2 and 3 describe the level of evidence for each of the interventions mentioned in the text, accordingly to the evidence grading system used in this review (Brainin et al. [7]).

#### Prevention of rebleeding

The main strategy to prevent rebleeding is to treat the aneurysm, excluding it from the arterial circulation. Should this be done by surgery (clipping) or through an endovascular procedure (coiling)? And how soon after the initial bleeding should it be done? Three other measures may decrease the risk of rebleeding: physical rest and avoidance of Valsalva's manoeuvre, blood pressure control and antifibrinolytics.

#### Clipping or coiling? (Fig. 6)

Two RCTs have been performed [43]. In the Koivisto et al. trial, which included 109 patients, clinical and neuropsychological outcomes at one year were comparable after early surgical and endovascular treatment. The ISAT trial [37, 61] showed that in patients with a ruptured intracranial aneurysm, for which endovascular coiling and neurosurgical clipping are therapeutic options, survival free of disability at 1 year was significantly better with endovascular coiling. This survival benefit continues for at least 7 years. The risk of seizures was also lower with coiling. Although the long-term risks of further bleeding are very low with either treatment they are somewhat more frequent after coiling.

Some important features of the ISAT trial should be considered when transposing its results into practice [9]. It followed the incertitude principle and therefore

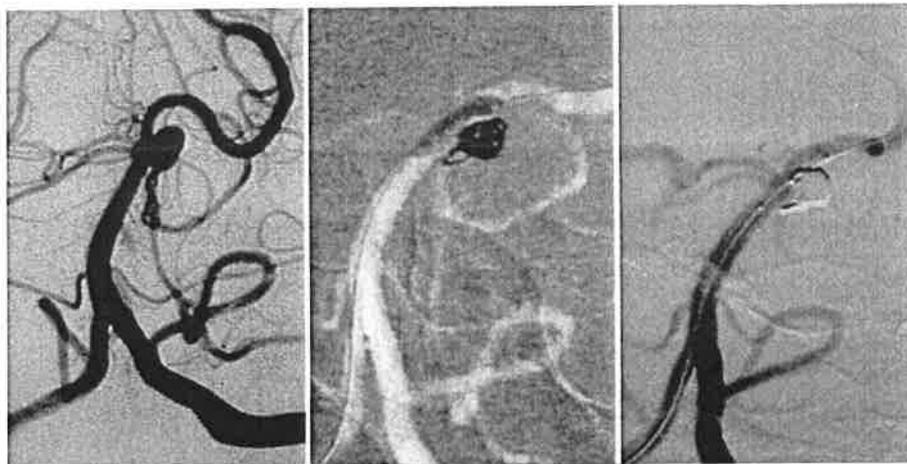
**Table 3** Treatment interventions for subarachnoid haemorrhage. Classification of levels of evidence (according to Brainin M et al. 2004) [6]

Treatment strategies	Evidence classification
Rebleeding, prevention	
Aneurysm treatment (surgical or endovascular)	II
Endovascular if both feasible early	
Early aneurysm treatment	III – surgical treatment IV – endovascular treatment
Avoidance of Valsalva manoeuvre, physical rest and blood pressure control	IV
Antifibrinolytics proved harmful	II
Vasospasm, prevention	
Nimodipine per os 60 mg 4/4 h	II
No benefit for triple H therapy	IV
Avoid hypovolemia	III
No benefit for tirilazad	I
Vasospasm, symptomatic	
Triple H therapy	IV
Balloon angioplasty (if refractory to medical treatment)	IV
Intra-arterial vasodilator (if refractory to medical treatment)	IV
Acute hydrocephalus	
Ventricular drainage	IV
Hyponatremia, prevention	
Fludrocortisone or hydrocortisone	III
Treatment with steroids	IV
Treatment strategies waiting further evidence	
Intracysternal thrombolytics for preventing vasospasm	
Intraventricular vasodilators for preventing vasospasm	
Nicardipine prolonged release implants for preventing vasospasm	
Antiplatelet agents for preventing vasospasm	
Statins for preventing vasospasm	
Endothelin antagonists for preventing vasospasm	
Intraventricular fibrinolytics for intraventricular haemorrhage	

many patients were treated surgically or by endovascular techniques outside the trial; it only included aneurysms of the anterior circulation; the majority of treated aneurysms were < 10 mm in size; patients were treated very shortly (mean 2 days) after the diagnosis, so the results cannot be generalised to centres where the endovascular procedures cannot be performed on an emergency basis. Finally, to transpose ISAT results into practice it is crucial to know the local figures for morbidity and mortality after coiling and clipping. The selection of the best treatment depends also on the morphology and location of the aneurysm (e.g. aneurysm with large necks are not convenient for coiling; posterior circulation aneurysms are best treated by endovascular techniques) [39, 51].

Incomplete treatment is more frequent after coiling. There is also less certainty concerning the long-term occlusion of the aneurysm. Therefore coiled patients need

**Fig. 6** Treatment of a basilar aneurysm by endovascular intervention. Untreated aneurysm (left). Due to the large neck of the aneurysm, a balloon was temporarily placed in the lumen of the artery while coils were detached to fill the aneurysm sac (centre). The treated aneurysm is excluded from the circulation (right)



periodically angiographic control, which should also be performed in clipped patients.

Based on the available evidence, it is recommended that in a patient with acute aneurysmal SAH in whom both treatments are feasible, coiling is the preferred choice [101], if it can be performed within 72 h after SAH.

There is considerable uncertainty regarding the best treatment options for SAH patients grades IV and V on admission. Evidence from case series in the literature, local practice results, ethical issues and cost should be taken into consideration. These patients have in general a poorer prognosis than patients in grades 0–III, but a subgroup appears to benefit from aggressive management (ICU care, ventricular drainage, angiography and endovascular or surgical treatment of the aneurysm) at a cost-effective ratio [110].

#### Early or late treatment?

There are two systematic reviews [18, 108] and a RCT evaluating the impact of time of surgery [68]. There are no studies of comparable quality in respect to endovascular treatment, nor in relation to specific subgroups of patients, such as those in poor condition and elderly patients. The evidence indicates that patients with aneurysmal SAH grades I–III should be treated as soon as possible (< 72 h) (evidence class III, for surgical treatment).

#### Treatment of blood pressure

There are no RCTs or systematic reviews on this topic. Reduction of blood pressure decreases the risk of rebleeding and increases the risk of ischaemia if vasospasm develops. An arbitrary cut-off of 180/100 mmHg is currently used in patients with untreated aneurysms, to treat BP.

#### Antifibrinolytic treatment

A systematic review of nine clinical trials was published [77]. Fibrinolytics decreased the probability of rebleeding, but increased cerebral ischaemia and consequently poor outcome. Therefore, available evidence (class II) does not support their use.

#### ■ Prevention of vasospasm and delayed cerebral ischaemia

There are three options to prevent and treat vasospasm: calcium channel blockers, triple H therapy (hypertension, haemodilution, hypervolaemia) and other treatments, including vasodilators, intracisternal thrombolytics, antiplatelets, neuroprotectors, statins, magnesium and endothelin antagonists.

#### Calcium channel blockers

There are several trials and five published meta-analyses evaluating the effect of calcium channel blockers (mainly nimodipine) in the prevention of vasospasm and delayed cerebral ischaemia [74].

Treatment with oral nimodipine, 60 mg 4/4 h, should be started immediately after the diagnosis and maintained for 21 days. Intravenous nimodipine is not recommended routinely due to potentially harmful decrease of blood pressure and because the majority of the trials used oral nimodipine.

Nicardipine prolonged-release implants were used successfully and safely for preventing vasospasm in a non-randomised, non-blind, controlled study [40, 41].

### Triple H therapy

The basis for the triple H therapy (hypervolemia, hypertension and haemodilution) is the finding that delayed cerebral ischaemia is enhanced by dehydration and limitation of fluid intake. Triple H treatment is used in the majority of the centres. It improves cerebral blood flow, but it remains unclear if it decreases delayed cerebral ischaemia. This therapy has several side effects, both neurological (cerebral oedema, rebleeding) and systemic (dilutional hyponatremia, cardiac failure with pulmonary oedema) [48, 84].

The evidence concerning triple H is poor. There is an inconclusive systematic review [97] and a meta-analysis of 2 small RCTs of hypervolemia with plasma expanders [74]. After the review three other RCTs trials were published. Again no benefit on functional outcome was demonstrated [22].

Hypovolemia should be avoided. Because of safety concerns, albumin should not be used. There is no evidence that hypervolemia is better or safer than normovolemia. If prescribed prophylactically as an option, triple H therapy should be limited to a few days to decrease the risk of complications. However it is more sensible to start triple H therapy when deficits develop and are thought to be related to vasospasm and delayed cerebral ischaemia.

### Other treatments

■ **Cysternal thrombolytics.** A meta-analysis [2] indicates a positive effect of this therapy in decreasing mortality and delayed cerebral ischaemia. However a RCT could not demonstrate such efficacy. There are insufficient data regarding safety of this intervention. New RCTs are necessary before direct cysternal injection of thrombolytics can be recommended as a routine. In any case this treatment can only be performed after coiling or clipping the aneurysm.

■ **Cysternal or intraventricular vasodilators.** In a non-randomised study with no controls sustained release papaverine was associated with a better functional prognosis [17]. Sodium nitroprussiate was used to prevent vasospasm in high risk patients and to treat refractory vasospasm, with no important side effects [93]. These treatments should be considered experimental.

■ **Antiplatelet agents and anticoagulants.** Following SAH there is an activation of platelet aggregation and an increased release of thromboxane A<sub>2</sub>, in particular in those who develop vasospasm. A systematic review indicated that aspirin produces a decrease in delayed cerebral ischaemia. The n<sup>o</sup> of patients was too small to allow conclusions regarding functional outcome and haemorrhagic risk [57]. Therefore, aspirin cannot be recom-

mended routinely in acute SAH. A single RCT of 170 patients with enoxaparin [85] showed that enoxaparin did not improve outcome but increased intracranial bleeding slightly.

■ **Statins.** Prior statin use was associated with better functional outcome in a matched controlled cohort study [69], although in another study statins were associated with an increased risk for vasospasm, probably due to abrupt statin withdrawal [86]. In a phase II RCT of 80 patients, pravastatin 40 mg/d was safe and reduced cerebral vasospasm, delayed ischemic deficits and overall mortality [98].

■ **Neuroprotectors.** Several RTCs tested the efficacy of free radical scavengers, namely the aminosteroid tirilazad, to prevent vasospasm. A meta-analysis of such trials concluded that tirilazad does not improve the outcome of SAH patients (class I) [20].

■ **New pharmacological treatments.** Several new compounds are undergoing pharmacological investigation as potential treatments for vasospasm and secondary ischaemia after SAH. Examples are nitric oxide donors, endothelin antagonists [99], potassium channel activators, erythropoietin [29, 38] and magnesium [100].

### ■ Treatment of established vasospasm and delayed cerebral ischaemia

Despite its limitation, transcranial Doppler is the most used and useful technique to monitor vasospasm. The following values of middle cerebral artery flow velocities are indicative of vasospasm: mean middle cerebral artery flow velocity > 120 cm/s (cut-off with highest negative predictive value) or > 200 cm/s (cut-off with highest positive predictive value) or a daily increase > 50 cm/s; the index middle cerebral artery/internal carotid artery should be > 3. Alternatives or complements to transcranial Doppler for monitoring vasospasm include single photon emission tomography, Xenon CT and novel devices such as a thermal diffusion microprobe [94].

If a patient with vasospasm develops symptoms the most commonly used treatment is the triple H therapy. If symptoms persist, endovascular interventions (intra-arterial vasodilators and/or balloon angioplasty) are used as a rescue treatment.

### Triple H therapy

Triple H therapy is routinely used to treat symptomatic vasospasm, despite lack of evidence from RCTs or systematic reviews [38]. There are several controlled and uncontrolled case series demonstrating that triple H

**Fig. 7** Acute hydrocephalus (left), treated by external drain (right)



therapy reverses vasospasm and its symptoms and a few trials of questionable methodological quality evaluating only one of the components of this therapy. In one R- and one quasi-RCT volume expansion failed to improve prognosis or to decrease the occurrence of secondary ischaemia and tended to increase the rate of complications. In another quasi-RCT hypervolemia reduced secondary ischaemia in the pre-operative period [74].

The surrogate goals of triple H therapy are to reach a central venous pressure of 8–12 cmH<sub>2</sub>O, 30–35% haematocrit and mean arterial pressure 20% above baseline, using IV crystalloids (e.g. 2000 ml 5% dextrose + 2000 ml normal saline or colloids (500–1000 ml)). Vasopressor amines (phenylephrine, dopamine, dobutamine) are used to raise blood pressure.

#### Endovascular treatment

■ **Ballon angioplasty.** In vasospasm refractory to medical treatment, arterial dilatation can be accomplished by balloon angioplasty [112]. This technique is effective in achieving proximal (but not distal) arterial dilatation, but is associated with risk of arterial rupture, re-bleeding and reperfusion syndrome. Despite several case series claiming optimistic results, there is only one controlled non-randomised retrospective case-study of 38 patients with neutral results [70].

■ **Intra-arterial vasodilators.** Intra-arterial injection of vasodilators has also been shown to reverse vasospasm. However, this effect is short-lived and these drugs can cause severe hypotension and brainstem depression. Some case series using AT877 and nimodipine [62] were reported, but there is only one non-randomised retro-

spective case-control study of 31 patients treated with intra-arterial papaverine [71].

### ■ Treatment of intraventricular haemorrhage and acute hydrocephalus

Acute hydrocephalus is a frequent complication of SAH. When symptomatic it can be treated with external ventricular drainage (Fig. 7). Repeated lumbar punctures are used in some centres although they carry the theoretical risk of re-bleeding if the aneurysm is not treated before. None of these therapeutic options was tested in clinical trials.

Intraventricular haemorrhage is associated with a poor prognosis, in particular if the amount of intraventricular blood is massive and there is accompanying hydrocephalus. In these cases clots can occlude the ventricular drain, making the relief of hydrocephalus more troublesome.

Some case series report the use of intraventricular fibrinolytics to prevent and treat hydrocephalus associated with intraventricular haemorrhage in SAH. Results are favourable when compared with non-treated patients, but the studies were non-randomised and the number of treated patients small. The meta-analysis of external ventricular drainage and fibrinolytics in SAH was inconclusive [66].

### ■ Steroids

Steroids are potentially useful in acute SAH by decreasing vasogenic oedema, inflammation and improving cerebral blood flow. However it is well known that they have a series of dangerous side effects, mostly increased risk of gastro-intestinal bleeding, infections and diabetes. A meta-analysis of three trials of steroids in SAH was unable to demonstrate evidence of either benefit or harm [24]. If steroids (e.g. dexamethasone 4 mg every 6 h for a few days) are prescribed, gastric protection with omeprazole or ranitidine should be used.

### ■ Treatment and prevention of hyponatremia

Hyponatremia is secondary to increased natriuresis. Vasopressin and desmopressin are commonly used to correct hyponatremia, despite the lack of evidence from RCTs. Several case series and controlled trials point out that hydrocortisone or fludrocortisone may be useful in the prevention of excessive natriuresis [30, 63, 64, 109].

Although oral NaCl 4–12 g/d, normal saline IV or hypertonic saline IV may be used to correct hyponatremia, they usually produce increased natriuresis and osmotic diuresis. Therefore, fludrocortisone 0.3 mg/d, 3x/d (class

IV) is the preferred option, when it is necessary to correct hyponatremia.

### ■ Treatment of SAH in particular subgroups of patients

#### Elderly patients

Despite the lack of information of good quality (no RCTs specifically designed for this age group, very few elderly patients included in RCTs of SAH treatment, no matched or stratified case-control studies) [33, 52, 67, 82, 88], the available evidence of case-series from centres in different world regions indicates that both surgical repair and endovascular treatment are feasible in this age group with acceptable rates of morbidity. Elderly patients more likely to benefit are those in good condition prior to the intervention [33, 52, 66].

#### Pregnancy

SAH during pregnancy is an important cause of maternal death. Ruptured aneurysms during pregnancy should be treated, surgically or by coiling. If the gestational age allows, it is better to carry out the delivery by caesarean before aneurysmal treatment [75, 83].

### Screening for new and asymptomatic aneurysms

Contrary to current beliefs, aneurysms are not congenital but develop continuously during lifetime. Unruptured aneurysms have a risk of rupture of ~1%/year, depending on their size.

Current evidence indicates that in patients with a life expectancy of at least 20 years, only those in the anterior circulation <7 mm should be left untreated. Screening for unruptured aneurysms is controversial [59].

#### Polycystic kidney disease

Patients with autosomal dominant polycystic kidney disease have a relative risk of SAH of 4.4% compared to the general population. Risk-benefit analysis failed to show any benefit of screening for unruptured aneurysms in these patients [28, 36].

#### Relatives of SAH patients

Screening with MR-angio or CT-angio for aneurysms in first degree relatives of SAH patients with more than one first degree relative with SAH or unruptured aneurysms is recommended by the American Heart Association 2000 guidelines. Angiography will reveal aneurysms in about 10%. Knowing to harbour an aneurysm has a negative impact in quality of life. The decision to screen

must incorporate the life expectancy and preferences of the person to be screened and the local complication rates for aneurysm treatment. In patients with familial aneurysm the motivation for screening appears to be high. Once the decision had been taken to screen an individual, screening probably needs to be repeated, because new aneurysms may develop and SAH has been described after an initial negative screening [107].

## SAH patients

In patients with aneurysmal SAH, new aneurysms develop at a rate of 0.28 to 1.62%/year for both de novo

aneurysms and for a second aneurysm [14]. In a decision model analysis Wermer et al. [106] found that the expected number of QALYs 10 years after clipping was the same for screening and for no screening. In general, screening for new aneurysms should not be recommended. However, in patients who fear a recurrence, screening increases QALY at acceptable costs. The identification of a subgroup of patients who have a high risk of aneurysm formation and rupture is necessary before screening can be recommended.

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**Orientado por:**

Nome do orientador

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