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Green Flags and headache: A concept study using the Delphi method

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Abstract: Objective: The aim of this study was to collect and rate Green Flags, that is, symptoms or pieces of information indicating that a patient is more likely to suffer from a primary than from a secondary headache. Background: When assessing headaches, a central question to be answered is whether the pain is primary or secondary to another disorder. To maximize the likelihood of a correct diagnosis, relevant signs and symptoms must be sought, identified, and weighed against each other. Methods: The project was designed as a Delphi study. In the first round, an expert panel proposed green flags that were rated anonymously in two subsequent rounds. Proposals with an average rating of 4.0 and higher on a scale from 0 to 5 reached consensus. Results: Five Green Flags reached consensus: (i) "The current headache has already been present during childhood"; (ii) "The headache occurs in temporal relationship with the menstrual cycle"; (iii) "The patient has headache-free days"; (iv) "Close family members have the same headache phenotype"; and (v) "Headache occurred or stopped more than one week ago." Conclusions: We propose five Green Flags for primary headache disorders. None being a pathognomonic sign, we recommend searching for both Green Flags and Red Flags. If both are present, a secondary headache should be suspected. Overall, the application of the Green Flag concept in clinical practice is likely to increase diagnostic accuracy and improve diagnostic resource allocation. Prospective studies in clinical populations should be conducted to validate these Green Flags. Keywords: diagnostic error; diagnostic uncertainty; primary headache; red flags; secondary headache.

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Green Flags and Headache

A concept study using the Delphi method

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Abstract

Objective: The aim of this study was to collect and rate Green Flags, i.e. symptoms or pieces of information indicating that a patient is more likely to suffer from a primary than from a secondary headache.

Background – When assessing headaches, a central question to be answered is whether the pain is primary or secondary to another disorder. To maximise the likelihood of a correct diagnosis, relevant signs and symptoms must be sought, identified, and weighed against each other.

Methods – The project was designed as a Delphi study. In the first round, an expert panel proposed Green Flags that were rated anonymously in two subsequent rounds. Proposals with an average rating of 4.0 and higher on a scale from 0 to 5 reached consensus.

Results – Five Green Flags reached consensus: (i) “The current headache has already been present during childhood”; (ii) “The headache occurs in temporal relationship with the menstrual cycle”; (iii) “The patient has headache-free days”; (iv) “Close family members have the same headache phenotype”; and (v) “Headache occurred or stopped more than one week ago.”

Conclusions – We propose five Green Flags for primary headache disorders. None being a pathognomonic sign, we recommend searching for both Green Flags and Red Flags. If both are present, a secondary headache should be suspected. Overall, the application of the Green Flag concept in clinical practice is likely to increase diagnostic accuracy and improve diagnostic resource allocation. Prospective studies in clinical populations should be conducted to validate these Green Flags.

Introduction

Headaches are common complaints of patients presenting to general practitioners, emergency-room doctors and neurologists. ¹⁻³ A common clinical approach is to first assess whether the headache is a primary headache disorder (e.g. migraine, tension-type headache) or secondary to another disorder (e.g. stroke, infection, tumour).⁴

Despite promising advances,⁵ there are no available biomarkers for primary headache disorders. Consequently, excluding a secondary aetiology is often about pondering probabilities. To maximise the likelihood of a correct diagnosis, clinicians identify and weight relevant cues against each other, all while respecting time constraints and resource limitations. Indications of secondary headaches – so-called “Red Flags” – are a prime example of these cues and have been investigated extensively.⁶ Less is known about “Green Flags”, i.e. signs or verbal cues pointing towards a primary headache disorder. The objectives for Red and Green Flags in headache care differ. The aim of the former is to raise the suspicion of a secondary headache – not to prove the diagnosis; thus, the higher its sensitivity the fewer cases will be missed. Conversely, the absence of a Red Flag with a very high sensitivity makes the diagnosis of a specific secondary headache unlikely, but not of a secondary headache in general.⁷ In practice, however, precise data on the sensitivity of Red Flags are often unavailable.⁶ In contrast, Green Flags should identify as many primary headaches as possible, but must avoid overlooking a secondary headache. The higher their specificity, the fewer potentially life-threatening disorders will be missed; the presence of a Green Flag with a high specificity makes a primary headache very likely.⁷ The absence of a Red Flag does not imply the absence of a secondary headache, because they are not pathognomonic signs.⁶ Therefore, we advocate looking for Green Flags in addition to Red Flags.

Red Flags are very regularly applied in various medical specialities. The use of Green Flags is not yet common, but should be considered more often. Usually, a physician’s primary objective when facing a medical problem is to diagnose the underlying disorder. Given that primary headaches are – in most settings – more common than secondary types,^{8,9} looking for Green Flags can help reaching that objective. The number of previously published Green Flags is small.⁸

It is thus the aim of this paper to provide a consensus recommendation on the use of Green Flags in headache disorders.

Methods

Study design – The project was designed as an online Delphi study and conducted from 6th October 2019 to 7th December 2019. The Delphi process is a method aiming at collecting and evaluating data as well as at reaching a consensus on their use.^{10, 11} In different rounds, participants proposed new data and then evaluated and re-evaluated the data gathered in previous rounds. Throughout the process, the ratings were cast anonymously; every participant's voice had the same weight. We conducted no statistical power calculation prior to the study; every member of the secondary headache interest group took part, hence, no higher number of participants was possible.

Definition of Green Flags – Before starting the Delphi process, all participants agreed on the following definition: "Green Flags in headache care are symptoms or pieces of information indicating that a headache patient is more likely to suffer from a primary headache disorder than from a secondary headache." In addition, we emphasised that Green Flags are positive findings – they do not merely indicate the absence of a Red Flag. Green flags were required to make a primary headache more likely; there were no predefined limits as to how much more likely they should be.

Expert panel – The expert panel consists of all members of the Secondary Headache Special Interest Group of the International Headache Society; they are experts in headache disorders from across Europe and the United States. The participants were informed by e-mail about the aim to provide a consensus recommendation on the use of Green Flags and gave their implicit consent by participating. In addition, every participant approved the final version of the article and gave their explicit consent to publish the article. Given that the Delphi method was solely used to organise the co-authors' thoughts, who were allowed to propose and rate Green Flags anonymously, the ethics committee's formal approval was not necessary.

Delphi process – In the first round, the expert panel listed Green Flags related to medical history, physical examination, laboratory findings, and imaging. The proposals were reviewed and – if identical to other suggestions – grouped together by one of the authors (HP). In case of a potential disagreement between the proposal and the definition of a Green Flag, the participants voted with a simple majority deciding about its elimination. Thus, we used the Delphi method to collect and rate Green Flags proposals but used a different approach to assess their compliance with a Green Flag definition.

In the second round, participants reviewed the list of Green Flag proposals and rated their quality according to predefined quality indicators. In the third round, participants considered the ratings of the second round and then re-rated the Green Flag proposals applying the same quality indicators used previously. Figure 1 provides an overview of the Delphi process used in this study.

Quality indicators – Participants estimated the quality of the proposed Green Flags based on clinical experience. To that end, we developed seven quality indicators (listed in Table 1). These aimed at estimating true and false positive rates (items 1 and 2), face validity (item 3), interpretational objectivity (item 4), procedural objectivity (item 5), random error (item 6), as well as the extent to which looking for the Green Flag would prolong the assessment (item 7). Each item was rated on a five-point Likert scale and assigned a score ranging from 1 to 5. We calculated a mean score for each quality indicator, summing the individual ratings and dividing them by the number of cast votes.

Total score – In order to compare the ratings of the Green Flags, we reached a total score by calculating the average from the mean scores of individual quality indicators; each quality indicator had equal weight.

Consensus criterion – We considered Green Flags with a total average score of 4.0 and above as having reached consensus.

Statistical analysis – This is the primary analysis of these data. The scores of the quality indicators are treated as continuous variables and described as means and standard deviations. In the second and third rounds, we calculated the total score for every quality indicator.

The statistical analysis was performed at the University Hospital Zurich using IBM SPSS statistics version 25.

Data Availability Statement – Qualified researchers can request the data collected during the study from the corresponding author.

Results

In the first round, 12 participants (response rate 100%) proposed 79 Green Flags. For seven of them, accordance with the definition of Green Flags and the requirement that these should be positive findings did not seem fulfilled. Therefore, the participants were asked to vote; ten participated (response rate 83%) and subsequently all doubtful proposals were eliminated. In addition, one of the authors (HP) grouped together identical Green Flags. In total, 41 proposals entered the next round. In the second round, ten participants (response rate 83%) rated the Green Flags; results are summarised in Table 2. In the third round, the participants were informed about the results of the voting in round two and were asked to re-rate them (10 participants; response rate 83%); results are summarised in Table 3. In total, five Green Flags reached consensus level; total scores including standard deviations are presented in Table 4.

Discussion

This study provides a consensus recommendation on the use of Green Flags in diagnosing headache disorders. In different surveys, proposals were collected, rated and re-rated. The expert panel identified five Green Flags (see Table 4) based upon estimates of both quality and relevance. The participation rate in all rounds was high and ranged between 83% and 100%.

Green Flags that reached consensus level were related to disease and headache duration, triggers, and family history. The expert panel rejected proposals related to pain intensity, accompanying symptoms, the patient's age, and comorbidities.

Green Flags

- A. The highest rating was assigned to **“The current headache has already been present during childhood.”** The underlying ideas were that (i) the duration of secondary headaches is usually limited and that (ii) dangerous secondary headaches generally reveal their threatening nature before long. During childhood, viral infections are the most common cause of secondary headaches¹² and in children with chronic headache, the pain is hardly ever secondary.¹³ While chronic post-traumatic headache does occur, it usually resolves within less than three years.¹⁴ It should be noted that medication overuse headache is common among children.¹⁵ Even though a life-threatening headache is very unlikely in adults in whom that headache type has already been present during childhood, a secondary headache due to medication overuse cannot be excluded. Let it be emphasised that this Green Flag has no clinical value in children as the underlying ideas (see above) do not apply in this age-group.
- B. **“The headache occurs in temporal relationship with the menstrual cycle,”** received the second-highest average rating. This Green Flag implies that the headache has occurred in the past and the relationship between pain and menstrual cycle has been validated, e.g. by a headache diary. Migraine attacks associated with changes in the menstrual cycle are very common.¹⁶ During the first three days of the menstrual cycle the probability of migraine without aura is significantly elevated.¹⁷
- C. **“The patient has headache-free days”** – refers to the intermittent nature of most primary headaches. Although intermittent secondary headaches may occur as well, they are often caused by trigger factors, such as injury to the head, whiplash, cerebral ischemia, intracranial haemorrhage, arteritis, arterial dissection or exposure to a substance, e.g. phosphodiesterase inhibitors, nitric oxide donors, or recreational drugs.¹⁸ An important exception are headaches associated with brain tumours that can also occur in non-daily attacks.¹⁹ It is important to note that the opposite – no pain-free days – is not considered a Red Flag;⁶ several primary headaches such as hemicrania continua, new daily persistent headache,

nummular headache, chronic tension type headache, chronic migraine, chronic cluster headache, chronic SUNCT, chronic paroxysmal hemicrania, and hypnic headache may occur daily as well.¹⁸

- D. **“Close family members have the same headache phenotype”** – suggests an inherited headache disorder or a headache disorder due to an inherited condition. The former is known to occur in cluster headache²⁰ and migraine;^{21, 22} the latter may occur in genetic vasculopathies, in which additional symptoms usually occur.²³ In addition, an increased familial risk for medication overuse headache has also been reported.²⁴ The prevalence of genetic vasculopathies (precise epidemiological data is unavailable) is very likely to be lower than that of cluster headache and migraine, and medication overuse headache is readily detected when looking for Red Flags. Thus, in the absence of a Red Flag, this Green Flag does point towards a primary headache.
- E. **“Headache occurred or stopped more than one week ago,”** refers to two principles.
First, dangerous secondary headaches generally reveal their threatening nature within days. Consequently, the more time passed since the headache, the smaller the probability that a life-threatening disorder caused it. However, time passed since onset of the headache is unlikely to influence the likelihood of a less dangerous secondary headache such as headache due to temporomandibular disorder, headache attributed to traumatic brain injury, or post-craniotomy headache.
Second, secondary headaches generally outlast their underlying cause; examples are headache attributed to traumatic brain injury, headache attributed to exposure to a substance, or post-craniotomy headache. Consequently, if the headache stopped more than one week ago, the likelihood of a dangerous secondary headache is low. The opposite – a persisting disorder despite abated headaches – does occur, though, e.g., in genetic vasculopathies,²³ vascular malformations,²⁵ and intracranial haemorrhages. The latter is important to keep in mind, as the average delay between a sentinel headache and a subsequent subarachnoid haemorrhage is 10.6 days ± 13.5.²⁶ In addition, the fact that a headache stopped does not exclude that it had initially been due to a less dangerous secondary headache.
Thus, even though this Green Flag generally points towards a primary headache, significant and potentially life-threatening exceptions may occur.

Remarks on the use of Green Flags

The Green Flag-concept seems to be a rather novel and literature about this approach is scarce. Therefore, we would like to highlight some aspects to keep in mind when using Green Flags in clinical practice.

1. The purpose of Green Flags is to identify as many primary headaches as possible while avoiding overlooking a secondary headache; to that end, a high specificity is mandatory.⁷ In this study, information on neither sensitivity nor specificity was available for any of the Green Flags; therefore, the participants estimated them based on their clinical experience (item 1 and 2; see Table 1). The highest estimate for specificity was reached by “The current headache has already been present during childhood”, “The headache occurs in temporal relationship with the menstrual cycle”, and “Close family members have the same headache phenotype” (see Table 3). These three Green Flags also had high total scores and reached consensus.
2. The odds of a primary headache disorder differ depending on the setting. Secondary headaches (most frequently due to infections) are common in primary care and more common than primary headache disorders in this setting.^{3, 27} However, the odds are higher for a primary headache disorder than a secondary headache in the hospital setting.^{8, 9.}
It is important to note that these prior probabilities strongly influence how reliably Green Flags (and Red Flags) identify primary (and secondary) headaches; Bayes’ theorem describes their relationship:²⁸

$$P(A|B) = \frac{P(B|A) * P(A)}{P(B)}$$

Here, *A* is the event of the patient suffering from a primary headache, and *B* is the event of the presence of a Green Flag with $P(B) \neq 0$. Furthermore, $P(A|B)$ denotes the probability of a

patient with a Green Flag suffering from a primary headache, and $P(B|A)$ the probability of a patient with a primary headache having a Green Flag.

It follows that the higher the probability of a primary headache disorder in a given sample, the higher the probability of a Green Flag correctly indicating a primary headache. In other words, the positive predictive value of a Green Flags is higher in a sample with many patients suffering from primary headache disorders than in a sample with a low number of patients with primary headache disorders.

When bearing prior probabilities in mind, the concept of Green Flags may help all physicians diagnosing headaches.

3. Patients suffering from a primary headache may need long-term follow-up; patients suffering from secondary headaches, on the other hand, need treatment of the underlying cause and sometimes solely a rapid intervention will save their lives. In general, given that the consequences of a secondary headache are potentially more severe, we recommend assuming a secondary headache, when both Green and Red Flags are present.
4. None of the Green Flags discussed here is likely to have a specificity of 100%; none is a pathognomonic sign of primary headaches. Therefore, they cannot be used as a shortcut to a headache diagnosis. However, many of the secondary headaches that might be missed by the Green Flags discussed above would have been detected by Red Flags.⁶ Thus, the positive predictive value of Green Flags is strongly increased in the absence of Red Flags. Consequentially, we recommend exploring for both Green Flags *and* Red Flags. Red Flags should always be given greater importance when both are present.
5. Finally, a thorough history is indispensable for making a correct headache diagnosis. If the collected information is unreliable, distinguishing primary from secondary headache becomes a matter of chance.

Strengths, limitations and future research

This study has two important strengths. First, it combines the expertise of several headache experts and resulted in previously unpublished Green flags originating from clinical experience. Second, ideas and hypotheses were generated freely without requiring sensitivity and specificity to be known beforehand. Therein, however, lies one limitation of the study; the ratings of the Green Flags were based upon the participants' experience – not on actual epidemiological data. To partly compensate for this limitation, we created quality indicators in close similarity to quality indicators of psychometric tests.²⁹ We intended to evaluate several aspects of their quality separately in order to reduce the random error. Since all were important, we decided to include them all into a total score.

Despite all efforts, one may interject that the proposed Green Flags do not necessarily point towards a primary headache disorder at all – rather, they modify the probability of the participants of this study diagnosing one. This objection could be addressed by validating these Green Flags in a prospective study, which we would like to propose for future research. As a result, the Green Flags approach could help to reserve imaging and costly examinations for patients with a high pre-test probability of a secondary headache and a low pre-test probability of a primary headache similar to what has been advocated by Choosing Wisely®.³⁰⁻³¹

Another limitation is the selection of the participants. Even though all of them have considerable theoretical knowledge about and practical experience in diagnosing and treating headache disorders, additional participants might have made different proposals or rated these proposals differently. Given that no paediatrician and no general practitioner took part, the ratings reflect the experience of neurologists treating adult patients.

Finally, we wish to emphasise that the task of diagnosing a headache disorder is not accomplished when the distinction between primary and secondary headaches has been made. Distinguishing primary from secondary headache does not necessarily distinguish harmless from dangerous. A treatment plan can only be worked out once the headache type has been diagnosed precisely.

Conclusions

In this study, we created a list of Green Flags that may be helpful to diagnose primary headache disorders, but need to be validated in prospective studies. This approach complements the search for Red Flags and can help increasing diagnostic accuracy. Furthermore, this is in line with a physicians' thinking that the aim of a consultation is to diagnose a disorder, not just to exclude grave differential diagnoses. Looking for Green Flags may be useful to prevent unnecessary additional investigations. Finally, we hope to encourage other experts to continue our discussion and start research on the concept of Green Flags.

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