1.1. Lamotrigine and alopecia - an update

Introduction

Lamotrigine (Lamictal®) is indicated for *the treatment of partial epilepsy and generalized epilepsy and for the treatment of syndrome of Lennox-Gastaut* in adults and children older than 12 years. In addition, in children of 2-12 years, the drug is indicated *as adjunctive therapy for the treatment of partial epilepsy and generalized epilepsy, as adjunctive therapy for the treatment of syndrome of Lennox-Gastaut and as monotherapy for the treatment of absence epilepsy.*

Furthermore lamotrigine is indicated in adults for *the prophylaxis of depressive episodes in patients with bipolar I disorder* [1].

Hair loss is a common clinical complaint, resulting from a wide variety of causes. Throughout life, hair follicles undergo cycling characterized by periods of growth (anagen), involution (catagen), and rest (telogen). Hair loss may occur due to disturbances of hair cycling, inflammatory conditions that damage hair follicles, or inherited or acquired abnormalities in hair shafts. Hair loss can occur diffuse or localized and be acute or chronic. It can also be caused by drugs by interference of the normal cycle of scalp hair growth. It can lead to two types of hair loss: a telogen effluvium (most common and usually appearing 2 to 4 months after start of drug intake) or an anagen effluvium (usually after a few days to weeks after drug initiation) [2].

In May 2007 Lareb described the association between alopecia and the use of lamotrigine in a quarterly report with 11 cases [3]. The current observation is an update of this association.

Reports

Between December 1997 and August 2014, the Netherlands Pharmacovigilance Centre Lareb received 22 reports of alopecia associated with the use of lamotrigine. Mostly diffuse hair loss was reported, one consumer reported alopecia areata. The reports were received from pharmacists (n=8), consumers (n=6), specialist doctors (n=4) and general practitioners (n=4). Eighteen reports concerned women and four reports concerned men. The median age was 33 years and ranged from 8 to 61 years. Time to onset was reported as ‘directly after start of the drug’ to 6.5 years (median latency three months). One patient recovered after stopping lamotrigine treatment. Seven patients did not change the medication and did not recover, two patients withdrew lamotrigine and did not recover, two patients increased the dose and did not recover and in ten patients the outcome was unknown.

In 17 reports lamotrigine was reported as the only suspect drug and no other drugs or causes were reported. In five reports concomitant use of (ox)carbamazepine or valproic acid, drugs known to cause alopecia [4,5], were reported. Other possible causes of alopecia reported in five reports were the use of lithium (however, this had been used for 7 years without any problems), the use of levothyroxine, weight loss, stress and a positive family history of hair loss [2,6,7].

Other sources of information

SmPC

The Dutch SmPC of lamotrigine does not mention alopecia [1]. The US SmPC describes alopecia as an infrequent adverse drug reaction [8].

Literature

In 2010 an article in Drug Safety was published about the observation of a continuous increase of case reports in Vigibase of alopecia in suspected connection to lamotrigine use. Lamotrigine was suspected of being involved in the development of alopecia in 337 patients, reported from 19 countries. The age of the patients ranged between 5 months and 84 years (mean 36 years), with a predominance (58%) of patients <40 years of age. 272 patients were female. In 291 reports, lamotrigine was the only drug suspected by the reporter, and in 112 reports, lamotrigine was the sole reported drug. Commonly co-reported drugs were other antiepileptic drugs. For 217 patients, alopecia was reported as the single event. In 11 patients, the reaction abated on cessation of lamotrigine. One patient was reported to have had a recurrence of alopecia on re-administration of lamotrigine [9].

Furthermore there are two case reports that describe alopecia with the use of lamotrigine.

A 63-year-old woman reported hair loss 2 to 3 weeks after beginning lamotrigine treatment. Blood tests and other laboratory parameters did not show pathological findings. The result of a hair root examination made by a dermatologist showed an increase of resting (telogen) and dystrophic hair at the expense of growing (anagen) hair. The hair loss was mainly located in the area of the temporal bone, which is characteristic for pharmacologically induced alopecia. Because of the probable association of the reported alopecia with lamotrigine treatment, the treatment was discontinued, which resulted in a rapid regression of hair loss [10].

Patrizi et al. [11] describe a 24-year-old woman who was treated with a combination of magnesium valproate and lamotrigine. The patient had taken sodium valproate for about 13 years and lamotrigine for about 2 years without hair problems. Hair loss started a few months after the dose of lamotrigine was increased and sodium valproate was replaced by magnesium valproate. A diagnosis of drug-induced telogen effluvium was made.

Databases

Table 1. Reports of alopecia associated with the use of lamotrigine in the Lareb, WHO and Eudravigilance database [12,13].

Database	Drug	Number of reports	ROR (95% CI)
Lareb	lamotrigine	22	3.7 [2.4-5.7]
WHO	lamotrigine	631	2.8 [2.6-3.1]
Eudravigilance	lamotrigine	137	1.8 [1.5-2.1]

Prescription data

Table 2. Number of patients using lamotrigine in the Netherlands between 2009 and 2013 [14].

Drug	2009	2010	2011	2012	2013
lamotrigine	16,720	17,237	17,752	18,506	19,153

Mechanism

Lamotrigine probably increases the resting (telogen) phase of hair cycling at the expense of the growing (anagen) phase [10].

Discussion and conclusion

In 2007 the Netherlands Pharmacovigilance Centre Lareb wrote a quarterly report about alopecia induced by lamotrigine. Then, Lareb had 11 case reports, now there are 22 case reports.

The association of lamotrigine and alopecia is supported by a statistically significant disproportionality in the database of Lareb, WHO and Eudravigilance.

In the literature, there are two case reports about lamotrigine induced hair loss and an overview with 337 cases in the WHO database. The Dutch SmPC does not mention alopecia, however the US SmPC does mention alopecia.

- Alopecia should be mentioned in the SmPC of lamotrigine

References

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This signal has been raised on July 2015. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl