Journal of the Neurological Sciences 331 (2013) 19–25

Contents lists available at SciVerse ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Review article

Bone disease during chronic antiepileptic drug therapy: General versus specific risk factors

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ARTICLE INFO

Article history:
Received 6 March 2013
Received in revised form 1 May 2013
Accepted 2 May 2013
Available online 21 May 2013

Keywords:
Anticonvulsant
Epilepsy
Bone disease
Bone mineral density
Fracture risk
Rickets
Osteopenia
Osteoporosis

ABSTRACT

An increasing number of studies suggest a direct effect of antiepileptic drug (AED) therapy on bone health: Patients on chronic AED therapy may have an increased risk of fractures, reduced bone mineral density, osteopenia, and osteoporosis. In an attempt to distinguish general and specific risk factors, this review examines the available empirical research. The pathophysiology is discussed and guidelines for early detection and treatment options are proposed.

Contents

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0022-510X/$ – see front matter
http://dx.doi.org/10.1016/j.jns.2013.05.005

1. Introduction

Epilepsy is a disease characterized by recurrent seizures and affects about 4 to 10 per 1000 persons in the general population. Antiepileptic drug (AED) therapy is the most common type of treatment, with nearly 70% of the patients eventually successfully achieving seizure remission [1]. Nonetheless, treatment with AEDs is generally chronic, if not lifelong, and has been associated with serious side effects on bone health, e.g. *increased fracture risk* [2–10], *rickets in children* [11,12], *decreased bone mineral density* [13,9,14–16], *osteopenia* [17–20,9,21,22,16,10,23], and *osteoporosis* [11,17,19–22,16,10].

Although the association between AED therapy and bone health has been recurrently reported, it appears difficult to confirm causality, since other major factors may lead to increased fracture risk and altered bone health in AED-treated patients. First of all, the increased fracture rate in patients on AED therapy may result from seizure-related trauma [24,25]. Also, antiepileptic drugs affect central nervous system (CNS) functions, possibly producing drowsiness, slowing of protective reflexes and incoordination, which often leads to falls and fractures, especially in the elderly [26–29]. Furthermore, hospitalization or institutionalization of patients with epilepsy may make them susceptible to many factors for low bone mineral density (BMD), e.g. lack of exposure to sunlight, limited physical activity and poor nutrition.

Many literature reviews have focused on the relationship between AED therapy and bone disease, with a focus on enzyme-inducing AEDs. However, conclusive evidence has not been reported. This article reviews the available empirical data on the prevalence of bone disease in AED-treated patients, to explore the relative risk of several factors. In a further attempt to clarify the relationship between AED therapy and bone health, a survey of postulated mechanisms is offered. We conclude with suggestions for early identification and intervention of altered bone health in patients treated with AED therapy.

2. Methods

2.1. Literature search

Relevant studies were identified by searching the electronic databases Cochrane, PubMed and ScienceDirect. Articles included in this review were identified by searching the following combination of MeSH terms: ("anticonvulsants" or "epilepsy") and ("fractures, bone", or "bone diseases"). This search resulted in 1826 publications. Titles of articles and abstracts extracted during the search were reviewed for relevance, and if found to be applicable, the full-text article was retrieved. For determination of incidence and risk ratios, only articles with experimental data were included. Articles obtained via citation tracking were also considered. Articles were included when published after 1960 up till 2012.

3. Results

3.1. Incidence and relative risk of bone disease during AED treatment

3.1.1. Fractures

Multiple empirical studies have evaluated the incidence of fractures during treatment with antiepileptic drugs, of which the results are summarized in Table 1. The risk of fractures is undoubtedly increased in AED-treated patients with epilepsy, with relative risk factors ranging from 1.3 to 6.1 [4–8]. Desai et al. [4] and Vestergaard et al. [7] eliminated seizure-related fractures from their relative risk analysis, and still found the risk of fractures to be increased in patients with epilepsy. Their results indicate that AED treatment contributes to the increased fracture risk, independent from the influence of the epilepsy itself.

3.1.2. Rickets

Rickets is a childhood condition which is characterized by insufficient amounts of vitamin D, calcium or phosphate in the bone matrix. The accumulation of unmineralized osteoid disturbs the mineralization of the growth plate of the bone. As a result, the bone does not become rigid and bends more easily. The mineral deficiency in the bones eventually causes destruction of the supportive matrix, resulting in progressive softening and weakening of the bones' structure. Symptoms can include bone pain and tenderness, dental problems, muscle weakness and severe skeletal deformities.

The incidence of rickets has greatly decreased after improved nutrition. It is now considered a rare disease, affecting less than 200,000 in the US population (National Institutes of Health). Although often the result of malnutrition—e.g. lack of vitamin D, calcium or phosphate—rickets has also been associated with AED treatment in children (Table 2). The two investigations identified by our literature search merely assessed institutionalized children with coexisting neurological

Table 1
Event rates and relative risk values of the occurrence of fractures in patients with epilepsy.

	EER	CER	RR
Pedersen et al. [2]			
–Patients with epilepsy	(14/87) 0.16		
Lindgren and Walloe [3]			
–Patients with epilepsy	(34/87) 0.39		
Annegers et al. [30]			
–Epilepsy vs. Expected CER			2.3
Desai et al. [4]			
–Epilepsy vs. Controls			4.2/3.4[a]
Jancar and Jancar [5]			
–Epilepsy vs. Controls	(18/68) 0.26	0.15	1.7
Scane et al. [6]			
–Epilepsy vs. Controls			6.1
Vestergaard et al. [7]			
–Epilepsy vs. Controls			2.0/1.3[a]
Persson et al. [8]			
–Patients with epilepsy	(20/177) 0.11		2.4
Souverein et al. (2005)			
–Epilepsy vs. Controls	(3478/40485) 0.09	(3940/80970) 0.05	1.9
Swanton et al. [9]			
–Patients with epilepsy	(112/208) 0.54		
Gniatkowska-Nowakowska [10]			
–Epilepsy vs. Controls	(43/126) 0.34	(19/132) 0.14	2.4
–Polytherapy AED vs. Monotherapy	(33/67) 0.49	(10/59) 0.17	2.9
Jefferson et al. [31]			
–Patients with Rett syndrome	(26/97) 0.32		

EER = Experimental Event Rate, CER = Control Event Rate, RR = Relative Risk (EER/CER).
[a] Relative risk ratio after elimination of seizure-related fractures.