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Kashin-Beck disease: from etiology to prevention or from prevention to etiology?

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Abstract The aetiology of Kashin-Beck disease (KBD) remains elusive. Four factors have been convincingly associated with the disease: selenium deficiency, iodine deficiency, grain contamination with mycotoxin-producing fungi, and water pollution with organic material and fulvic acid. The most credible studies from a scientific standpoint, i.e. randomised placebo controlled trials and observational cohort studies have either not been conducted or did not provide unequivocal demonstration in favour of any of these hypotheses. Many studies such as case-control, cross-sectional, “before-after”, and even more so, ecological studies have been conducted. They merely produced weak evidence and fail to support any single factor to the exclusion of the others. The most scientifically sound studies have included animal models, laboratory experiments and pathology studies; however, these have only provided indirect evidence. Although none of the competing theories prevails when they are compared using a predefined and standard set of causality criteria (temporality, strength of the association, biological gradient, experimental evidence, biological plausibility, coherence, specificity and analogy), none should be discounted. This is an indication that a comprehensive and unifying theory is most likely to be multifactorial. Because the ultimate goal of those who are compelled by the challenge of KBD is to prevent its occurrence, a perfect understanding of its mechanisms is not indispensable for action. Well-conducted randomised intervention should be the priority of researchers as well as public health professionals to demonstrate what works and what does not.

Résumé L'étiologie de la maladie de Kashin-Beck (KBD) demeure vague et incomplète. Quatre facteurs

sont cependant associés sans ambiguë à la maladie: le déficit en sélénium, le déficit en iode, la contamination des céréales par des mycotoxines et la pollution de l'eau par des matières organiques et l'acide fulvique. Les études les plus crédibles d'un point de vue scientifique que sont l'essai clinique randomisé et l'étude de cohorte n'ont pas été réalisées ou ont montré des résultats équivoques. Elles ne donnent pas d'avantage clair à l'une de ces hypothèses. De nombreuses autres études cas-témoins, transversales, “avant-après”, et davantage encore des études écologiques ont été réalisées. Elles ont seulement documenté des associations discutables et n'ont pas permis d'écarter l'un ou l'autre de ces quatre facteurs étiologiques. Les études les plus rigoureuses scientifiquement s'appuient sur des modèles animaux, des expériences de laboratoire et des données anatomo-pathologiques. Elles n'ont produit que des évidences indirectes. Bien qu'aucune des théories en présence ne domine nettement lorsqu'elles sont évaluées à l'aune de critères de causalité prédéfinis (la temporalité, la force de l'association, le gradient biologique, l'évidence expérimentale, la plausibilité biologique, la cohérence, la spécificité et l'analogie), aucune ne peut cependant être exclue. Ce constat indique qu'une théorie explicative globale qui prendrait en compte tous ces éléments est probablement multifactorielle. Dans la perspective ultime de la prévention la maladie de Kashin-Beck, une connaissance détaillée des mécanismes étiologiques n'est pas indispensable pour agir. Des interventions randomisées bien conduites et bien documentées devraient être la priorité des chercheurs et des professionnels de la prévention. Elles seules permettront de distinguer ce qui utile et indispensable de ce qui ne l'est pas.

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Introduction

Although Kashin-Beck disease (KBD) was described more than 100 years ago and continues to affect communities throughout Asia and the Himalayas [18], it remains a disease of uncertain aetiology. The contrast be-

tween high prevalence and morbidity [19], and the outstanding absence of productive aetiologic research [1] remains a unique feature of KBD. Several reasons may account for this unfortunate state of affairs. KBD is a disease of poor rural populations and, often, minorities. It is not considered transmissible and only concerns isolated areas that have little contact with densely populated urban centres. It has not been described in industrialised countries where most resources for medical research are available. Last but not least, the disease, because it is complex and probably multifactorial, presents a great scientific challenge. Many research teams involved with KBD have been working in isolation whereas the key to disease aetiology may come from the collaboration of individuals and groups with expertise in a variety of domains and the pooling of their knowledge and experimental findings.

The proof of causality, i.e. the demonstration that a given cause is responsible for a given effect, is a complex and lengthy process. No unique study or experiment, no unique evidence or design can ever be sufficient to conclude beyond any reasonable doubt that A causes B. After the classical elements of the Henle-Koch postulate [20], a more complete set of causality criteria have been developed [4] and discussed [17]. They provide a useful frame of reference to distinguish causal and noncausal associations, a tool to assess competing theories. This formal approach and even the fulfilment of these criteria, however, do not preclude a pragmatic approach to disease prevention. In fact, prevention interventions may provide additional clues if their efficacy is well documented.

In this paper, we will briefly describe the main aetiologic hypotheses of what may cause KBD. We assess and classify evidence supporting these hypotheses and discuss the extent to which available evidence supports each of these hypotheses. This brief review does not intend to be comprehensive but to provide a framework to assess the contribution of past and current research to the discovery of KBD aetiology.

Aetiology

Most authors consider selenium deficiency to be the culprit. Selenium is a component of an enzyme that plays an important role in protecting chondrocytes from lipid peroxidation initiated by mycotoxins and fulvic acid [14, 15, 16]. In the absence of selenium, they would contribute to the alteration of chondrocytes, the primary lesion of KBD. Iodine deficiency causes hypothyroidism and cretinism. Thyroid hormones are indispensable to chondrocyte metabolism. For this reason, iodine deficiency in combination with other factors has been suggested as an important aetiologic agent of KBD [13, 21]. Fungal contamination of grains may produce mycotoxins. These, in turn, would generate free radicals, which would interfere with chondrocyte metabolism and cause KBD. Contamination of drinking water with organic material such as fulvic acid would be responsible through the same mech-

anism, i.e. the production of free radical carriers [16, 29]. Other factors including vitamin C or E deficiency [16], other micronutrient deficiencies, unknown infectious agents and genetic factors have been considered potential possibilities for KBD aetiology [6].

However, the disease, seems unlikely to be due to only one agent or one cause. Even if this was the case, or if KBD turns out to be an infectious disease due to a unique agent, other host and environmental factors are likely to confer a relative protection or, to the contrary, to facilitate or accelerate the disease. These risk and protective factors may be the key to future prevention strategies. Although the most likely hypothesis is multifactorial, and no individual factor is likely to cause KBD alone, KBD aetiology is yet to be investigated comprehensively. Various combinations of factors may be necessary and yet not sufficient, depending on other, unknown genetic or environmental factors. Various elements may have a specific role at various points of the causal pathway and interaction between causal components may be at play.

Types of supporting evidence

Not all scientific evidence has the same weight when it comes to the proof of causality. The strongest evidence is provided by randomised, possibly placebo-controlled clinical trials. Observational cohort studies are second best, ahead of case-control studies. Major problems with such studies are the possibility that unknown selection and information bias distort the results. In addition, it is sometimes difficult to be absolutely sure that exposure preceded the disease in case-control studies. This problem is exacerbated in cross-sectional studies. In the absence of randomisation and control group "before-after" studies may be used as weak surrogates. With this design, however, it is not known what would have occurred in the absence of intervention. It is therefore impossible to attribute any observed difference to the intervention. Ecological studies compile and compare observations made in various environments, regions or countries, and correlate the presence of an exposure in these environments with the prevalence of disease. The evidence provided is even less credible than in the studies already mentioned. Case studies, in which only patients are described are useful for suggesting hypotheses but useless for studying causality. In contrast, animal models, laboratory experiments, studies of pathology and molecular biology are all critical to the proof of causality. When studying the aetiology of human diseases, however, they must be considered together with epidemiological studies, as the evidence they provide is always indirect with respect to the proof of causality.

Causality criteria

The definite demonstration that a given cause is responsible for a given disease is long and complex. Hill [4]

and more recently Rothman and Greenland [17] have proposed an assessment of putative causes with the following set of well-defined criteria. The first and only indispensable criterion is *temporality*: the exposure to the causal factor must precede the disease in time. The *strength* of the association or the correlation between exposure and disease is commonly measured with the relative risk or the odds-ratio. An exposure factor associated with a tenfold-increased risk of disease, for example, is more likely to be causal than a factor associated with a doubling of the risk. *Biologic gradient* or *dose-response* refers to the fact that the risk of disease increases with the amount, the duration or the intensity of the exposure. The risk of lung cancer, for example, increases with the cumulative number of cigarettes smoked. *Consistency* refers to the repeated observation of an association across various independent studies conducted in different populations and under different circumstances. *Experimental evidence* refers in general to animal experiments. It is considered less important than the other criteria because there are always many possible explanations to experimental results. *Biological plausibility* represents the fact that the hypothesis is acceptable given the current biologic knowledge. *Coherence* indicates that the interpretation of the cause and effect relationship agrees with what is known of the natural history and the biology of the disease. *Specificity* is fulfilled if the exposure is always present with the disease and the disease never occurs in the absence of exposure. This criterion essentially applies to infectious agents and is rarely completed with non-communicable diseases. Finally, *analogy* means that

there is some similarity between the hypothesis tested and some other biological process.

Evidence and causality criteria

Table 1 describes how the four leading hypotheses of KBD aetiology have been investigated. It is striking that no randomised trial or cohort studies have produced convincing evidence to substantiate any of these hypotheses. The most thoroughly explored theory using various study designs is selenium deficiency. Conflicting results, however, have been reported. Iodine deficiency is a relatively recent hypothesis and has only been studied and implicated in one case-control study [13]. Ecological studies, i.e. regional comparisons have been conducted to assess the putative role of both grain contamination and mycotoxins, and organic pollution of water. These two hypotheses have also been investigated with various levels of success using cross-sectional survey. Various other factors have been studied with case-control studies, before-after comparisons, experimental studies, animal model and ecological studies [5, 6]. None, however, as extensively as the four already discussed.

An assessment of causality criteria for the four KBD aetiological factors is presented in Table 2. Temporality, the simplest and most critical, has not been clearly demonstrated for any factor. This is the result of the lack of well-conducted prospective cohort study or randomised trial. KBD has been strongly associated with grain contamination and mycotoxin, and to a lesser extent with io-

Table 1 Kashin-Beck disease aetiology: Main hypotheses for suspected causal factor and supporting evidence

Evidence	Credibility	Selenium deficiency	Iodine deficiency	Mycotoxin/fungi	Fulvic acid/water
Randomised trial	+++	Not conclusive [10, 11, 28]	–	–	–
Cohort study	++	[28]	–	[28] and quoted in [6]	[28]
Case-control study	+	[13]	[13]	–	–
Cross-sectional survey	+	–	–	[2]	[29]
Before-after intervention	+/-	[7, 8, 10, 23]	–	–	–
Ecological studies	+/-	[3, 9]	–	[25, 26]	[29]
Animal models	+/-	[12]	–	[27]	–
Laboratory experiment and pathology	+	[24]	–	–	[22, 30]

Table 2 Kashin-Beck disease aetiology: Main hypotheses and fulfilment of causality criteria

Causality criteria	Selenium deficiency	Iodine deficiency	Mycotoxin/fungi	Fulvic acid/water
Temporality (in human studies)	No	No	No	No
Strength	+/-	+	++	No
Biologic gradient	No	No	No	No
Consistency	+/-	No	No	No
Experimental evidence	+/-	No	+/-	No
Biological plausibility	Yes	Yes	Yes	Yes
Coherence	Yes	Yes	Yes	Yes
Specificity of cause	No	No	No	No
Analogy	No	No	Yes	No

dine deficiency and selenium deficiency. Dose-response has not been documented with any of the hypotheses. Experimental evidence is available for selenium deficiency and mycotoxin. Both biologic plausibility and coherence are fulfilled to some extent by all four putative factors. Obviously specificity, a less important criteria, is out of reach for all factors.

It is probable that these factors interact to produce KBD. Selenium deficiency, for example, may be indispensable for the disease to occur but, as is always the case with "universal exposure", it does not emerge as a risk factor when studied in a population that is globally selenium deficient [13]. A complete integrating theory would be difficult to assess. It is conceivable that the consequence of iodine deficiency in combination with selenium deficiency, in the presence of an oxidative stress due to exposure to specific mycotoxins or organic contamination of water, produces or favours KBD. If this is the case, none of the four factors discussed in this article may cause KBD alone. Only a prospective randomised controlled trial will produce definite proof of this integrative theory. It would test the individual and combined effects of complementary interventions on iodine, selenium, grain and water, for example.

Admittedly, this review is incomplete and biased towards articles published or translated in English. It pays too little tribute to the majority of original research conducted in the field of KBD in the past hundred years [1]. The objective of this brief article, however, is to provide a framework to assess competing theories against a common set of criteria. Our inability to definitely disprove the role of selenium, iodine, mycotoxin and organic pollution probably reflects the multifactorial aetiology of KBD. Depending on the relative prevalence of any of these factors and the protective effect of competing causes, the others may become either indispensable or barely necessary.

The ultimate goal of those who are compelled by the challenge of KBD may not be to prove what causes this disease. Indeed, it is to prevent disease occurrence and, hopefully, make it a historical curiosity. Public health professionals did not need a perfect understanding of the mechanisms of smallpox pathogenicity and genome to eradicate the disease. Well-conducted randomised intervention studies of KBD should be the priority of researchers and public health activists.

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